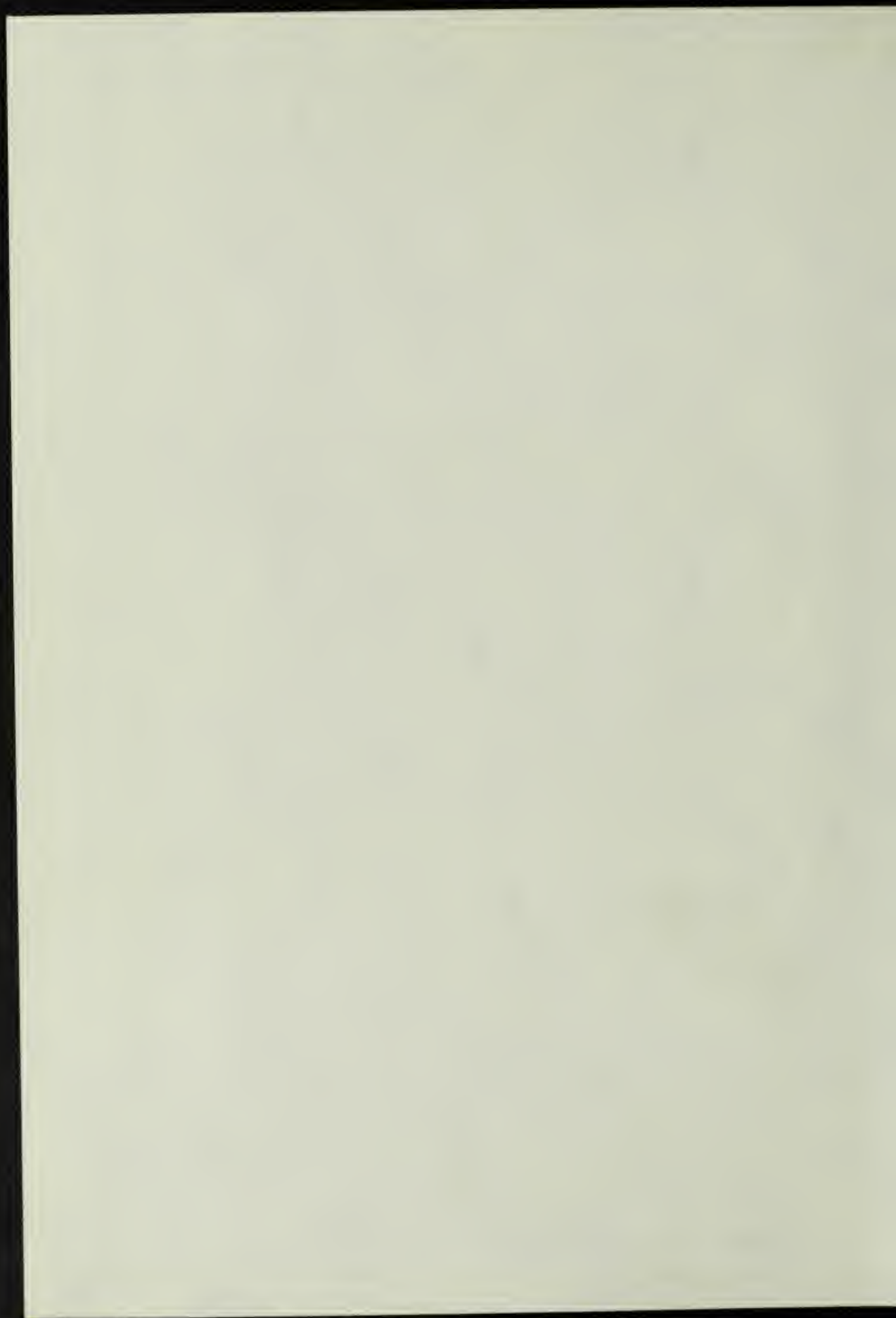
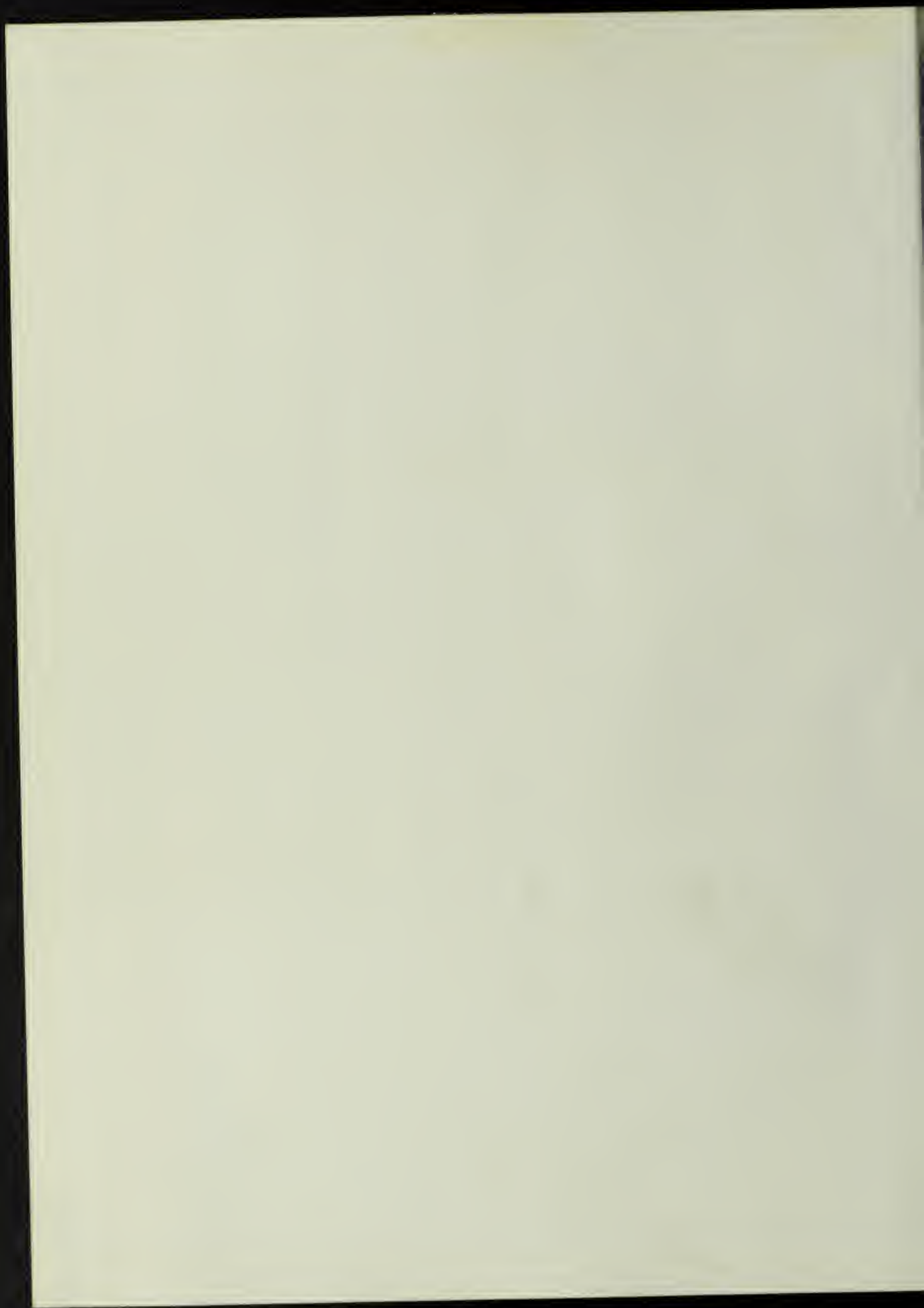

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CARCINOGENESIS ABSTRACTS

VOLUME 15,
ISSUE 10



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CARCINOGENESIS ABSTRACTS

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EDITOR

GEORGE P. STUDZINSKI, M.D., Ph.D.
COLLEGE OF MEDICINE AND DENTISTRY
OF NEW JERSEY, NEWARK

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RUTHANN E. AUCHINLECK, *Managing Editor*

The Franklin Research Center
The Benjamin Franklin Parkway, Philadelphia, Pennsylvania 19103

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CARCINOGENESIS ABSTRACTS**VOLUME 15, ISSUE 10****CONTENTS**

	Cross Reference Abbreviations	Article Numbers	Page
REVIEW	(Rev)	77-5401-7705461	1919
CHEMICAL CARCINOGENESIS	(Chem)	77-5462-77-5648	1931
PHYSICAL CARCINOGENESIS	(Phys)	77-5649-77-5697	1970
VIRAL CARCINOGENESIS	(Viral)	77-5698-77-5853	1980
IMMUNOLOGY	(Immun)	77-5854-77-5893	2014
PATHOGENESIS	(Path)	77-5894-77-5926	2023
EPIDEMIOLOGY AND BIOMETRY	(Epid-Biom)	77-5927-77-5962	2029
MISCELLANEOUS	(Misc)	77-5963-77-6000	2037
AUTHOR INDEX			2043
SUBJECT INDEX			2053
CHEMICAL ABSTRACTS SERVICE REGISTRY NUMBER INDEX			2117
WISWESSER LINE NOTATION INDEX			2121

GENERAL INFORMATION

CARCINOGENESIS ABSTRACTS makes available abstracts, annotations or citations of significant carcinogenesis articles collected from the current major biomedical sources of world literature. This service is provided by the National Cancer Institute through a contract with the Franklin Research Center for preparation of the publication, under Contract No. NOI-CP-75885 with the National Cancer Institute, U.S. Department of Health, Education and Welfare. Published and distributed by the Franklin Institute PressSM.

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ORIGINAL ARTICLES

1. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
2. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
3. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
4. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
5. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
6. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
7. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
8. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
9. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
10. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1

CONTENTS OF THIS ISSUE

1. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
2. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
3. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
4. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
5. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
6. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
7. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
8. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
9. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1
10. The Effect of the Diet on the Blood Sugar in the Normal Individual and in the Diabetic Patient	1

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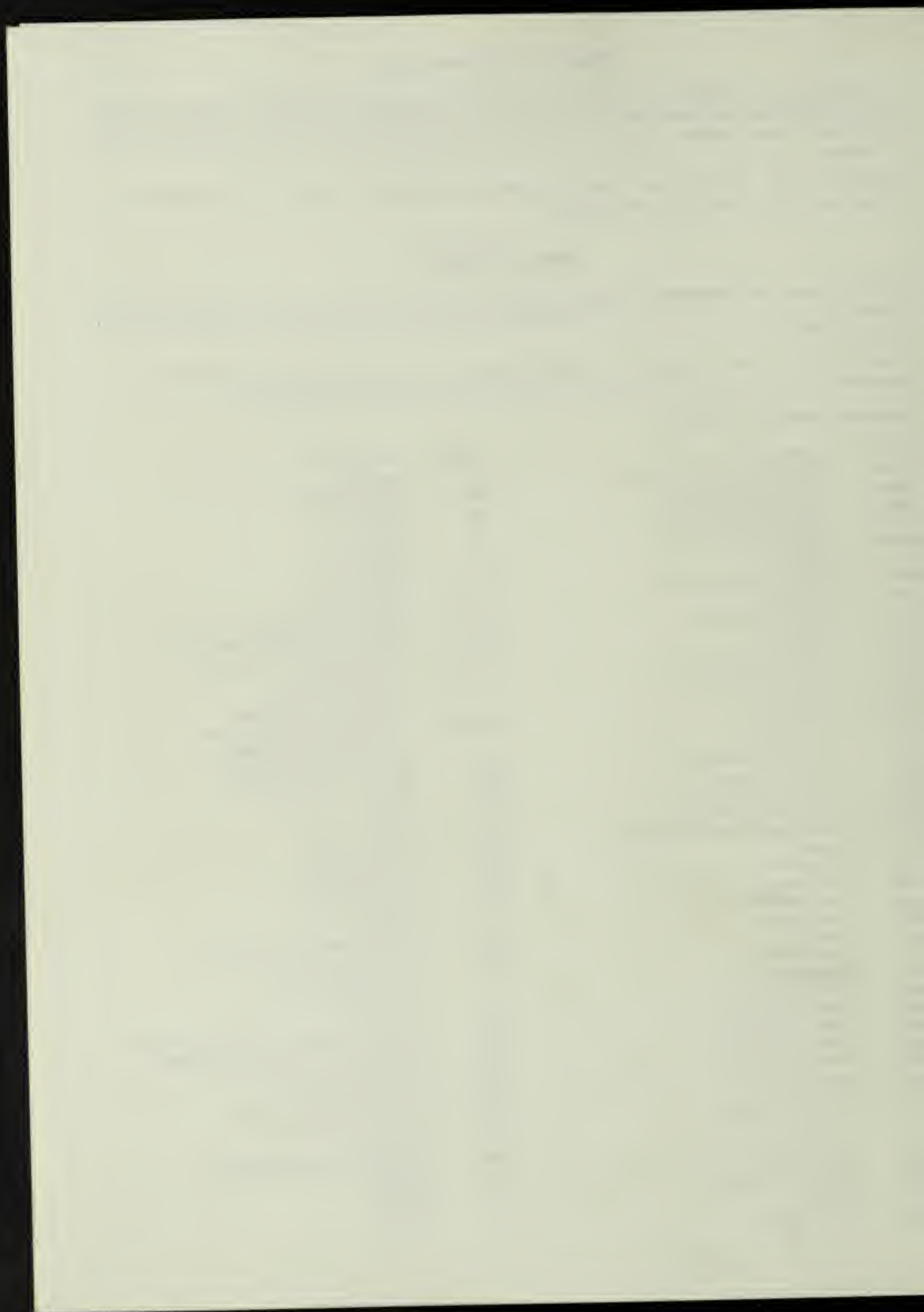
ABBREVIATIONS

JOURNAL names are abbreviated according to the *List of Journals Indexed in Index Medicus, Abbreviation Listing*. If the journal is not listed in this, abbreviations are derived from the *International List of Periodical Title Word Abbreviations*.

LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED ₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO ₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intradermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD ₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD ₅₀	median lethal dose		
M	molar		
μM	micromolar		



REVIEW

7-5401 **Some Problems Associated with the Testing for Environmental Mutagens and a Perspective for Studies in "Comparative Mutagenesis."** (Eng.) Sobels, F. (Dept. Radiation Genetics, Univ. Leiden, Netherlands). *Mutat Res* 46(4): 245-260; 1977.

In evaluating the effects of mutagenic chemicals, one can distinguish four phases: (1) primary identification or detection of mutagenic activity; (2) verification; (3) quantification; (4) extrapolation to man. For primary identification of a particular compound as a mutagen, fast bacterial assay systems are most suitable. Regulatory measures ought to be postponed until mutagenic activity has been verified from at least two other assay systems. The micronucleus assay is the simplest and fastest test for the detection of chromosome-breaking activity with short-term cultures of human lymphocytes in vitro. Detection systems that make use of differences in electrophoretic mobility are being developed. Extrapolation of results to man presents problems, as chemical mutagens are highly specific with respect to the spectrum of genetic changes, organisms, or cell types. Assessment of the genetic risks involved requires a quantification in terms of dose-effect curves. In the absence of suitable fast tests for gene mutation in intact mammals, however, these cannot yet be determined. The approach to assessing genetic damage in humans consists of a series of stepwise comparisons for different end-points of genetic damage at different concentration levels, a modification of the parallelgram. (84 refs.)

7-5402 **Global Distribution of Carcinogenic Pollutants in Water.** (Eng) Kraybill, H. F. (Cancer Cause and Prevention, NCI, Bethesda, MD 20014). *Ann NY Acad Sci* 298: 80-89; 1977.

Data are presented on the concentrations of recognized or suspected carcinogens identified in drinking water supplies in the US, Netherlands, and Canada. Organic carcinogenic contaminants found in water supplies worldwide are listed. Geographic variations in the distribution of environmental pollutants, the biomedical significance of carcinogenic contaminants, and directions for future research are discussed. The presumptive evidence of carcinogenicity from studies on marine animals should be linked with epidemiologic surveys of cancer incidence by organ sites and by regional areas. Further studies on concentrated mixtures and fractions of water contaminants are also necessary to establish causal relationships to cancer. (35 refs.)

7-5403 **Part I. Occurrence and Removal of Water Pollutants. Analysis of Organic Compounds in Wa-**

ter to Support Health Effects Studies. (Eng) Garrison, A. W. (Environmental Res. Lab., U.S. Environmental Protection Agency, Athens, GA 30601). *Ann NY Acad Sci* 298: 2-19; 1977.

Current methods of measuring organic compounds in water are discussed and illustrated by their application to volatile organic pollutants in New Orleans drinking water, purgeables in Miami drinking water, and volatile organics in industrial effluents and municipal sewage. Advances in the analytic methodology for volatile compounds are noted, and suggestions are made for developing analysis of nonvolatile compounds, which account for up to 95% of the total organic material in water. The establishment of the environmental Protection Agency's computerized library of organic water pollutants is reviewed briefly. (25 refs.)

77-5404 **Role of the Registry of Tumors in Lower Animals in the Study of Environmental Carcinogenesis in Aquatic Animals.** (Eng) Harshbarger, J. C. (Registry Tumors in Lower Animals, Natl. Museum Natural History, Smithsonian Institution, Washington, DC 20560). *Ann NY Acad Sci* 298: 280-289; 1977.

The distribution of neoplastic and nonneoplastic lesions recorded at an aquatic animal tumor registry since 1966 is tabulated. Neoplasms accounted for slightly more than half of the 10,000 tumor specimens received; they occurred in both fresh- and saltwater species, particularly in bottom feeders. Presumably, carcinogenic chemicals absorb to particulates that settle at the bottom, increasing the exposure of species such as filtering and detritis-grazing mollusks and scavenging fish. A table lists seven animal groups and their tissue system of origin of the neoplasms; cell types from nearly every determined system in reptiles, amphibians, and fish were capable of neoplastic transformation. Also listed are the several aquatic populations, the type of neoplasm they contained, and their specific habitats. In laboratory experiments, fish and shellfish were susceptible to chemicals that are carcinogenic for mammals and metabolize them in a similar manner. (78 refs.)

77-5405 **Discussion Paper: Enigmas of Cancer in Relation to Neoplasms of Aquatic Animals.** (Eng) Stewart, H. L. (Registry Experimental Cancers, NCI, Bethesda, MD 20014). *Ann NY Acad Sci* 298: 305-315; 1977.

The use of neoplasms in aquatic animals for detecting environmental carcinogens and for identifying animal models for carcinogenesis studies is evaluated. Tumors have been identi-

fied in fin fish and shellfish at one or more of the following sites: skin, gill, mantle, oral region, pharynx, stomach, pancreas, liver, kidneys, gonads, heart, thyroid, nervous system, soft tissues, skeleton, and lymphoreticular and hematopoietic tissues. The Northern Pike in particular provides a unique model for the study of etiologic and environmental relationships in hematopoietic neoplasms. The hematopoietic neoplasms of the mollusks may be useful in studying the evolutionary development of neoplasms, and the schwannomas of snappers may provide a model for von Recklinghausen's disease. (25 refs.)

- 77-5406 Neoplasms in Rainbow Trout, a Sensitive Animal Model for Environmental Carcinogenesis.** (Eng) Sinnhuber, R. O. (Dept. Food Science and Technology, Oregon State Univ., Corvallis, OR 97331); Hendricks, J. D.; Wales, J. H.; Putnam, G. B. *Ann NY Acad Sci* 298: 389-408; 1977.

When present as glycerides in cottonseed oil, meat, and flour, cyclopropanoid fatty acids (malvalic acid and sterulic acid) greatly enhanced the incidence and growth of aflatoxin B₁ (AFB₁)-induced hepatocellular carcinoma in rainbow trout. Subsequent studies showed (1) that dietary proteins may have an important role in the biotransformation of AFB₁ to aflatoxicol, (2) that basophilic nodules are the principal line of neoplastic development in trout liver, and (3) that the trout embryo may be a sensitive model for screening mycotoxins and other potential carcinogens. (82 refs.)

- 77-5407 Distribution of Neoplasms and Other Diseases in Marine Fishes Relative to the Discharge of Waste Water.** (Eng) Mearns, A. J. (Southern California Coastal Water Res. Project, El Segundo, CA 90245); Sherwood, M. J. *Ann NY Acad Sci* 298: 210-224; 1977.

A study of approx 290,000 fish collected from southern California coastal waters between 1969 and 1976 showed that 5% were affected with fin erosion, tumors, color anomalies, or attached macroparasites. Fin erosion, which occurred at the highest frequencies and in the greatest number of species, was the only disease that appeared to be directly associated with the discharge of municipal wastewaters. Neither the lip papillomas of the white croaker nor the epidermal tumors of young Dover sole were related to single municipal wastewater discharge sites or to other discrete sources of pollutants. No skin tumors were observed in other pleuronectids, and the prevalence of lip papillomas in white croakers was lower than in past years. The prevalence of Pacific sanddabs with *Phrixecephalus cincinnatus* increased with distance from the Palos Verdes shelf, suggesting that the high chlorinated hydrocarbon levels in the tissues of fish at Palos Verdes are inimical to this attached macroparasite. (37 refs.)

- 77-5408 A Review on the Toxicity of Trace Amounts of Tetrachloroethylene in Water.** (Eng) Utzinger, R. (Inst. Toxicology, Swiss Federal Inst. Technology, CH-8003 Schwerzenbach, Switzerland); Schlatter, C. *Chemosphere* 6(9): 517-524; 1977.

The toxicity, metabolism, mutagenicity, carcinogenicity, and environmental concentrations of tetrachloroethylene (C₂Cl₄) are discussed. The ingestion or inhalation of 50 mg/day C₂Cl₄ is considered acceptable; therefore, the trace amounts of C₂Cl₄ in air and drinking water are not a serious health problem. Mice exposed to the compound for 12 mo (300 or 600 ppm, 6 hr/day 5 days/wk) developed liver cancers, but these results could not be extrapolated to humans. (22 refs.)

- 77-5409 Confidence Intervals and Test of Hypotheses Concerning Dose Response Relations Inferred from Animal Carcinogenicity Data.** (Eng) Crump, K. S. (Dept. Mathematics, Louisiana Tech. Univ., Ruston, LA 71272); Guess, H. A.; Deal, K. L. *Biometrics* 33(3): 437-451; 1977.

The statistical methodology involved in the low-dose extrapolation of data from animal studies conducted at high doses to humans is reviewed. Confidence intervals and hypothesis tests are presented based on data from animal carcinogenicity experiments. Likelihood ratio tests are developed for the presence of a positive dose-related effect and for the existence of a positive slope to the dose-response curve at zero dose. The programs described should be useful not only in analyzing animal carcinogenicity data but also in improving the statistical design of these experiments and the selection of appropriate doses. (18 refs.)

- 77-5410 In Vitro Testing for Chemical Toxicity: Marquisian Target Cells (Meeting Abstract).** (Eng) Waters, M. D. (Environmental Protection Agency, Research Triangle Park, NC 27711); Huisingsh, J. L. *In Vitro* 13(3): 192; 1977. (no refs.)

- 77-5411 In Vitro Assessment and Mechanism of Action of Environmental Pollutants.** (Eng) Hart, R. V. (Dept. Radiology, Coll. Medicine, Ohio State Univ., Columbus, OH 43210); Hays, S.; Brash, D.; Daniel, F. B.; Davis, M. T.; Lewis, N. J. *Ann NY Acad Sci* 298: 141-158; 1977.

The correlations between DNA damage and carcinogenesis and the processes of prereplication, strand-break, and postreplication repair of DNA damage are discussed. In addition, a method is described for the direct measurement of carcinogen- or mutagen-induced DNA damage and repair. T

method, which is based on recording the fluorescence of chloroacetaldehyde-DNA products as a function of DNA concentration, may eventually provide a rapid prescreen for environmental mutagens and carcinogens. (94 refs.)

77-5412 **Metal Carcinogenesis.** (Eng) Sunderman, F. W. (Dept. Lab. Medicine, Univ. Connecticut Sch. of Medicine, Farmington, CT). In: *Advances in Modern Toxicology*. Goyer, R. A.; Mehlman, M. A., eds. (New York: John Wiley & Sons): Vol. 2, Toxicology of Trace Elements, 33 pp.; 257-295; 1977.

Epidemiologic and experimental studies of the carcinogenic potential of metallic compounds are summarized. Epidemiologic studies have demonstrated an increased incidence of specific cancers among workers exposed to arsenic, chromium, and nickel compounds. In experimental animals, cancers have been induced by compounds of eight metals (beryllium, cadmium, chromium, cobalt, lead, nickel, zinc, and iron carbohydrate complexes). The carcinogenicity of nickel subsulfide (Ni_3S_2) is greater than that of any other metallic compound. A single im injection of 5 micromoles into Fischer rats produced a 77% incidence of malignant sarcomas within 20 days. Nickel and beryllium compounds become localized in rat cell nuclei, and they exert acute inhibitory effects on mitosis and the expression of genetic information. These effects may be related to the molecular mechanisms by which metallic compounds induce malignant transformation. (260 refs.)

77-5413 **Oral Contraceptives and Endometrial and Cervical Cancer.** (Eng) Moghissi, K. S. (C. S. Mott Center Human Growth and Development, 275 E. Hancock, Detroit, MI 48201). *J Toxicol Environ Health* 3(1/2): 243-255; 1977.

Prolonged administration of estrogens or sustained production of unopposed endogenous estrogenic substances may be associated with an increased risk of endometrial hyperplasia and atypical adenomatous hyperplasia leading to well-differentiated endometrial adenocarcinoma. Apparently, the development of endometrial cancer does not depend on the presence of the ovaries or the administration of estrogen, since the cancer occurs in women with dysgenetic ovaries and surgical castrates who have never received exogenous estrogen. Endogenous estrone, on the other hand, does appear to play a role and its precise function needs to be investigated. Progestogens bring about regressive changes of the hyperplastic and cancerous endometrium. Development of endometrial cancer in users of steroidal contraceptives has been reported. On the basis of current data, no cause-and-effect relationship between these compounds and endometrial neoplasia can be assumed. However, oral contraceptives, particularly those of sequential formulations, do not protect suscep-

tible users against endometrial cancer. Studies have failed to demonstrate an increased incidence of abnormal cytologic smears, cervical dysplasia, or cancer in women receiving oral contraceptives. However, initial surveys have found a difference in prevalence rates of abnormal smears among women using oral steroids as opposed to other modes of contraception. (82 refs.)

77-5414 **The Aetiology of Breast Cancer and the Oestrogenic Metabolites of Fusaria (Meeting Abstract).** (Eng.) Schoental, R. (Dept. Pathology, Royal Veterinary Coll., Univ. London, London, England). *Br J Cancer* 36(3): 427-428; 1977. (3 refs.)

77-5415 **The Role of Hormones on Digestive and Urinary Tract Carcinogenesis.** (Eng) Yamamoto, R. S. (Carcinogen Metabolism and Toxicology Branch, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20014); Weisburger, E. K. *Recent Prog Horm Res* 33: 617-653; 1977.

Experimental results are reviewed in attempt to relate sex differences in cancer incidence to hormonal influences. Particular attention is focused on the involvement of the sex and pituitary hormones in the genesis of liver tumors, which are more common in men. The review of urinary tract carcinogenesis includes preliminary work on hormonal enhancement of renal tract carcinogenesis. A brief summary of the role of hormones in carcinogenesis in other organs is presented. Hormones play a role both in the activation of the carcinogen to its ultimate carcinogenic form and possibly during the growth of the latent tumor into differentiated and undifferentiated ones. It is not known which stage is affected more. (131 refs.)

77-5416 **Tobacco and Alcohol Consumption in Relation to the Development of Multiple Primary Cancers.** (Eng) Wynder, E. L. (American Health Foundation, 1370 Ave. Americas, New York, NY 10019); Mushinski, M. H.; Spivak, J. C. *Cancer [Suppl]* 40(4): 1872-1878; 1977.

The relationship between tobacco use and alcohol consumption and the development of additional primary cancers of the upper alimentary tract is reviewed. The chance of developing a second primary depends principally on the intensity (ie, quantity and duration) of the smoking and drinking habit prior to the onset of the first neoplasm. However, results conflict regarding the effect exerted by the continuation of these habits after the first diagnosis. Although smoking is the primary risk factor associated with cancers in this area, its

interaction with alcohol creates a powerful carcinogenic effect. It is agreed that multiple primaries are selective on a site-specific basis and that risk varies with anatomic location of the first primary. (20 refs.)

- 77-5417 **Occupational Cancer: Questions and Answers.** (Eng) Nicholson, W. (NCI Conference on Cancer Epidemiology and the Clinician, Boston, MA); Cole, P.; Schneiderman, M. *Cancer [Suppl]* 39(4): 1807-1808; 1977.

In this discussion of occupational carcinogenesis, topics include the risk of polyvinyl chloride-induced cancers at low doses; asbestos, smoking and mesotheliomas; and bladder cancers. It is estimated that 10% to 15% of all cancers are due to occupational exposure and that 85% to 90% are environmentally induced. (no refs.)

- 77-5418 **PAN in the Natural Environment; Its Possible Significance in the Epidemiology of Skin Cancer.** (Eng.) Lovelock, J. E. (Univ. Reading, Reading, Berks., England). *Ambio* 6(2/3): 131-133; 1977.

It is hypothesized that tropical air may carry high concentrations of peroxy acetyl nitrate (PAN) and other possibly carcinogenic organic compounds, which could be a contributing factor in the increased incidence of skin cancer in these areas. Precursors of PAN in the normal troposphere may undergo photochemical conversion, producing potentially harmful concentrations of the chemical. (8 refs.)

- 77-5419 **Radiation-induced Carcinoma of the Lung--The St. Lawrence Tragedy.** (Eng) Wright, E. S. (Dept. Surgery, Memorial Univ. Newfoundland, St. John's, Newfoundland, Canada A1C 5S7); Couves, C. M. *J Thorac Cardiovasc Surg* 74(4): 495-498; 1977.

The problem of radiation-induced lung cancer in the fluor-spar miners of Newfoundland is reviewed. Seventy-eight workers have died from this disease since commercial operation began in 1933. In 1959, the source of the radiation was identified as radon and its daughter nucleotides which are present in the water seeping into the mines. Heavy smoking is probably synergistic with the radiation. The histology of the tumors in this group of workers is unusual, since squamous cell carcinoma accounts for 90% of the cases. There have been four patients with second primary lung cancers. Radical radiotherapy has been the primary mode of treatment, based on the reluctance of the miners to undergo operation. Surprisingly good results have been obtained, with an

av survival of 34 mo after treatment. Institution of improved ventilation has reduced radiation to safe levels, but an estimated 120 miners from the pre-1960 era are still at risk. (no refs.)

- 77-5420 **Action of UV and Visible Light on Nucleic Acids and Proteins.** (Ger.) Lober, G. (Zentralinstitut für Mikrobiologie und experimentelle Therapie, Abteilung Biophysikochemie der Akademie der Wissenschaften der DDR, Jena, E. Germany). *Z Gesamte Inn Med* 32(6): 133-138; 1977.

Three photochemical reactions that might cause changes in biologic materials are discussed: (1) photoreactions induced by UV light in nucleic acids and proteins; (2) photoreaction induced by UV light in cell constituents not belonging to the natural biologic system; ie, furocoumarins and carcinogenic hydrocarbons; and (3) photoreactions induced in sensitizer molecules that absorb UV or visible light. The latter reaction consumes molecular oxygen but not the sensitizer molecule (photodynamic action). Photodynamic changes in the blood may be caused by exogenous sensitizers or sensitizers that are constituents of the blood itself, such as porphyrins. (83 refs.)

- 77-5421 **Experimental Ultraviolet Light-Carcinogenesis.** (Eng) Black, H. S. (Dept. Dermatology, Baylor Coll. Medicine, Houston, TX 77030); Chan, J. T. *Photochem Photobiol* 26(2): 183-199; 1977.

Recent developments in experimental UV light (UVL) induced carcinogenesis are reviewed and discussed in terms of the major theories concerning this process. Quantitative studies have led to the impression that UVL-mediated carcinogenesis involves two integral steps: the first involving a reversible genetic change in the cells (akin to somatic mutation) and the second, an acceleration of cell proliferation. Three mechanisms have been advanced to explain UVL induced carcinogenesis: DNA damage and/or its repair by photochemical reactions, and lysosomal lysis. None can be favored as yet because of a lack of conclusive experimental evidence but the most attractive is the one involving DNA damage and repair. Certain relationships have been noted between diet and UVL carcinogenesis. Epidemiological data have indicated that individuals whose diets contain high levels of cholesterol and who have had excessive sun exposure are predisposed to skin cancer. Dietary fats, other than cholesterol, also enhance UVL carcinogenesis, but dietary antioxidants afford protection against the process. Although the data are not conclusive, the results of immunological studies suggest that UVL is capable of suppressing the normal immunological system, allowing tumor growth. (265 refs.)

77-5422 **The Epidemiology of Herpes Simplex Diseases.** (Ger.) Schneweis, K. E. (Institut für Med. Mikrobiologie und Immunologie, Universität Bonn, 5300 Bonn, Germany). *Z Hautkr* 52(7): 427-432; 1977.

The epidemiology of herpes simplex virus (HSV) is discussed, with emphasis on the importance of its persistence as a latent infection in ganglion cells. In this state, the virus cannot be attacked by the body's defense system. Nerve conduction is involved in the reactivation of the latent virus. Because the organ and tissue specificity of HSV types 1 and 2 are bound to the entire pathogenetic complex, type 1 remains epidemiologically the facial virus and type 2 the genital virus. Antibodies against HSV type 2 are more frequently demonstrated in patients with cervical carcinoma. Comparative examinations have shown that increased exposure is not the sole cause of this prevalence. However, the relationship between herpes genitalis and cervical carcinoma remains unclear. (10 refs.)

77-5423 **The Role of Herpes Viruses in Human Tumours (Meeting Abstract).** (Eng) de-The, G. (CIRC, Lyon, France). In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 0; 1977. (no refs.)

77-5424 **Viral Lymphomagenesis in the Domestic Fowl: A Review.** (Eng) Payne, L. N. (Houghton Poultry Res. Station, Huntingdon, Cambridgeshire, PE17 2DA, England). *Proc R Soc Med* 70(8): 559-562; 1977.

A review of the pathogenesis, epidemiology and vaccination potential of Marek's disease and lymphoid leukosis (virally induced lymphomatous diseases of domestic fowl) are presented. Marek's disease is caused by a herpesvirus which is spread horizontally from bird to bird. Genetic resistance to the disease is recognized, but the mechanism is unclear. Vaccination has reduced the worldwide incidence by > 80%. Lymphoid leukosis can be prevented by early surgical removal of the bursa of Fabricius. The viruses can be transmitted either as infectious particles or as endogenous viruses within the host DNA. No vaccines have been developed, and it is questionable whether one is feasible against a vertically transmitted infection in which there is immunological tolerance to viral antigens. (1 refs.)

77-5425 **Has the src Gene Product Been Found?** (Eng.) Weiss, R. (ICRF Lab., London, England). *Nature* 269(5626): 287; 1977.

Several recent experiments are briefly reviewed that may lead to the identification of the avian sarcoma virus (ASV) src gene protein. A transformation specific antigen has been found in ASV-transformed cells. The src gene is necessary for the fibroblast transformation and sarcoma induction, but is superfluous for viral replication. (5 refs.)

77-5426 **Viruses of Eels With and Without Stomatopapillomas.** (Eng) McAllister, P. E. (Eastern Fish Disease Lab., Fish and Wildlife Service, U. S. Dept. Interior, Kearneysville, WV 25430); Nagabayashi, T.; Wolf, K. *Ann NY Acad Sci* 298: 233-244; 1977.

The characteristics of the viruses (eg, rhabdovirus and orthomyxovirus) isolated from eels with or without stomatopapillomas are reviewed. Neither the viruses nor extracts from diseased eels induced tumors in healthy fish. The occurrence of stomatopapilloma in eels may be linked to a latent or slow virus infection that is activated by stress caused by industrial water pollutants. (31 refs.)

77-5427 **Immunology of Experimental Liver Cell Cancer.** (Eng.) Baldwin, R. W. (Cancer Res. Campaign Labs., Univ. Nottingham, Nottingham, NG7 2RD, England); Price, M. R. In: *Liver Cell Cancer*. Cameron, H. M.; Linsell, D. A.; Warwick, G. P., eds. (New York: Elsevier Scientific Publishing Co.) pp. 203-242; 1976.

Current knowledge of the immunology of experimental hepatic tumors induced by chemical carcinogens is reviewed, with emphasis on the nature and characteristics of tumor-associated antigens. There is evidence that neoantigen expression in liver neoplasms is characteristic of carcinogen-induced tumors in general. (156 refs.)

77-5428 **Genetic Analysis of Malignancy Using Somatic Cell Hybrids.** (Eng.) Minna, J. D. (NCI-VA Medical Oncology Branch, Veterans Admin. Hosp. and NCI, Washington, DC 20422). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy 3: 343-354; 1977.

A review is presented of past research and current standards using hybridization of cells to study genetic regulation of neoplastic behavior. Problems encountered with oncogenic viruses and in vivo tumor studies are discussed. (88 refs.)

- 77-5429 **View of a Mammalian Cancer Geneticist.** (Eng.) Heston, W. E. (Lab. Biology, NCI, NIH, Bethesda, MD 20014). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy 3: 475-479; 1977.

The murine mammary tumor virus system is used as a model for illustrating how genetic techniques can be used to investigate the causative factors that lead to the malignant transformation of cells. (17 refs.)

- 77-5430 **A General Theory of Carcinogenesis.** (Eng.) Comings, D. E. (Dept. Medical Genetics, City of Hope Natl. Medical Center, Duarte, CA 91010). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy 3: 387-389; 1977.

A general framework is briefly outlined for viewing tumor cell biology from the genetic standpoint. The close relationship between carcinogenesis and mutagenesis is confirmed. (4 refs.)

- 77-5431 **Are Nonrandom Karyotypic Changes Related to Etiologic Agents?** (Eng.) Rowley, J. D. (Dept. Medicine, Univ. Chicago, Chicago, IL 60637). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy, vol. 3, 519 pp.; 125-136; 1977.

It is hypothesized that specific chromosomal abnormalities in human tumors may be related to particular etiologic agents. Chromosome banding techniques have shown nonrandom chromosomal abnormalities in chronic myelogenous leukemia and in acute leukemia. It appears that only certain chromosomes are abnormal in a particular tumor and that these same chromosomes may be aneuploid in a variety of tumors. Nonrandom chromosomal abnormalities occur in some animals exposed to chemical and viral mutagenic agents. When leukemia, sarcomas, and epithelial tumors were induced by 7,12-dimethylbenz(a)anthracene (DMBA) and 6,8,12- and 7,8,12-trimethylbenz(a)anthracene in rats, trisomy for the largest telocentric chromosome was observed. A different but very consistent karyotypic pattern was seen in sarcomas induced in the rat by Rous sarcoma virus. These observations suggest that the specific chromosomal abnormalities are associated with particular etiologic agents. In the rat, the order of carcinogenic potency is DMBA, methylcholanthrene, and benzo(a)pyrene, in decreasing order; the frequency of nonrandom changes shows the same order. It

has been suggested that, if a given mutagen is more potent as a carcinogen, it may attack certain genes more selectively in the induction of malignancy. Several human tumors are associated with known environmental carcinogens, but none of these otherwise rare tumors have been studied cytogenetically. Tumors suggested for such investigation are thyroid carcinoma, in those received therapeutic x-rays in the neck region, lung and gastric cancer in asbestos workers, oat cell cancers of the lung in workers exposed to halo ethers, hepatic angiosarcoma in vinyl chloride workers, clear cell adenocarcinoma in women exposed to diethylstilbestrol in utero, and urinary bladder carcinoma in workers exposed to polycyclic aromatic compounds. (45 refs.)

- 77-5432 **Some Current Models of Carcinogenesis.** (Eng.) Lowdin, P. O. (Quantum Theory Project, Univ. Florida, Gainesville, FL). *Int J Quantum Chem Quantum Biol Symp* (4): 185-196; 1977.

The virus, somatic mutation, and reading-error models of carcinogenesis are reviewed in the context of a genetic theory that postulates that DNA regulates both DNA replication and protein synthesis through a two-step "reading" process (transcription and translation). The electronic theory of cancer is also discussed in this framework. Cancer is probably caused by a disturbance in the cell-differentiation control system. The details of this disturbance may provide the final clue for the understanding of viral, radiation, or chemical carcinogenesis. Some current models of aging are examined in this connection. (14 refs.)

- 77-5433 **Human Disease with In Vitro Manifestations of Altered Repair and Replication of DNA.** (Eng.) Cleaver, J. E. (Lab. Radiobiology, Univ. California, San Francisco, CA 94143). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy. 3: 355-363; 1977.

A number of diseases characterized by defects in DNA repair mechanisms are discussed relative to some general theories of carcinogenesis. Xeroderma pigmentosum is cited as an illustration of the mutational theory that malignancy results from defective repair of UV-induced damage to skin cells. (47 refs.)

- 77-5434 **Nosology among the Neoplastic Genodermatoses.** (Eng.) Lutzner, M. A. (Dermatology Branch, NCI, NIH, Bethesda, MD 20014). In: *Genetics*

Human Cancer. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy, Vol. 3, 519 pp.; 1977.

Genetic skin diseases associated with cancer are considered. Xeroderma pigmentosum (XP) and albinism are two autosomal recessive genodermatoses in which sunlight causes cancer. Black patients with XP have a much higher mortality than albinos, indicating that the DNA repair system (which is defective in XP) is a more critical protective mechanism than pigment production. Epidermodysplasia verruciformis is an autosomal recessive genodermatosis in which the wart virus may cause squamous cell carcinoma. Ataxia-telangiectasia (AT), Bloom's syndrome, and Fanconi's syndrome are all autosomal recessive diseases associated with chromosomal instability. Patients with these disorders have a high risk of leukemia. AT, Wiskott-Aldrich syndrome, Bruise's disease, Swiss-type agammaglobulinemia, and gastrointestinal lymphangiectasia are all associated with immunological abnormalities in addition to increased susceptibility to cancer. Patients with the Chediak-Higashi syndrome have a mutation of skin, hair, and eye pigment and often die young from a lymphoma-like "accelerated" phase. Nevroid basal cell carcinoma syndrome is a disease that appears to result from abnormalities of the neural crest. Neurofibromatosis (von Recklinghausen's syndrome) and tuberous sclerosis (Pringle's disease, epiloia, and adenoma sebaceum) are also classified as neurocristopathies and have an increased risk of cancer. Porokeratosis, a skin disease associated with abnormal keratinization, is associated with squamous cell carcinomas. Another such disease, tylosis, carries a high risk of esophageal cancer. Polyposis associated with genodermatoses and an increased risk of cancer include Gardner's, Peutz-Jeghers's, and Cowden's syndromes (multiple hamartoma syndrome) and the blue rubber bleb nevus syndrome. Congenital abnormalities of the skin associated with neoplasia are giant pigmented nevus, nevus sebaceous of Jadassohn, and nevus of Ota. (76 refs.)

77-5435 **Cytogenetics of Human Neoplasia.** (Eng.) Harnaden, D. G. (Dept. Cancer Studies, Univ. Birmingham, Birmingham, England). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy, Vol. 3, 519 pp.; 87-104; 1977.

The role of chromosomal change in predisposition to malignancy and the significance of chromosomal abnormalities in cancer cells are reviewed. Ionizing radiation leads to chromosome damage, including clone formation, and tumors induced by radiation show chromosomal changes, but so far chromosome damage induced by radiation has not been linked with that seen in radiation-induced tumors. Viruses are suggested to cause chromosome rearrangements are associated with production of neoplasms; some viruses regularly lead to

stem line proliferation, but others produce continuing instability. The association of some constitutional chromosome aberrations with neoplasia, eg, Down's and Klinefelter's syndromes, may be indirect and due to hormonal imbalance or other physiologic factors. The chromosome breakage syndromes (Fanconi's anemia, Bloom's syndrome, and ataxia telangiectasia) and those with DNA repair defects may exert their effects by generating a population of enormous cellular diversity. Environmental agents may also lead to the production of a population of variable unstable cells. Clones of cells with malignant potential may be selected from within this population of unstable cells by an interplay between the cells and the host response. Clones of cells may form prior to the onset of neoplasia and could indicate the establishment of cells with a proliferative advantage in which a neoplastic population could arise. As people grow older, they may accumulate areas with populations of cells (some clonal) having abnormal chromosomes; these areas may be the regions prone to neoplasia. Nonrandom chromosomal changes have been observed in certain types of cancer, specifically leukemia, testicular tumors, Burkitt's lymphoma, and meningiomas. (123 refs.)

77-5436 **Genetic Repertory of Human Neoplasia.** (Eng.) Mulvihill, J. J. (Clinical Epidemiology Branch, NCI, Bethesda, MD 20014). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy. Vol. 3: 137-143; 1977.

A table is given that lists > 200 neoplasms as single-gene traits or as a feature of complication of other Mendelian disorders. The type of inheritance and associated neoplasms (if any) are included for each neoplasm or disorder. The table is long, as a substantial number of single-gene traits in humans can be manifested as neoplasia; it emphasizes the large number of genes that might be involved in cancer susceptibility (1/2 the traits are autosomal dominant, 1/3 autosomal recessive, and 1/6 X-linked); and it includes nearly all the histologic types of tumors. (21 refs.)

77-5437 **Cancer and Inbreeding.** (Eng.) Schull, W. J. (Center for Demographic and Population Genetics, Univ. Texas Health Science Center, Houston, TX 77030). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy, Vol. 3, 519 pp.; 15-17; 1977.

Examples are cited of inbred populations prone to specific cancers. It is suggested that inbreeding could increase the frequency of neoplasia by increasing the number of homozy-

gotic individuals, who respond to a lesser level of environmental stimulation. (8 refs.)

77-5438 Chromosome Instability Syndrome. (Eng.)

Hecht, F. (Crippled Children's Div. and Perinatal Medicine, Univ. Oregon Health Sciences Center, Portland, OR 97201); McCaw, B. K. In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F., eds. (New York: Raven Press): Progress in Cancer Research and Therapy, Vol. 3, 519 pp.; 105-123; 1977.

The chromosome instability syndromes are divided into two groups, classic and new. The classic syndromes, which were described before 1970 include Bloom's syndrome, Fanconi's syndrome, ataxia-telangiectasia (AT), and xeroderma pigmentosum. Primary cancer develops in 1/6 patients with Bloom's syndrome, with about half the cancers being non-lymphocyte leukemias. Fanconi's syndrome is accompanied by an increased risk of acute leukemia, especially the myelomonocytic form. Affected patients are also at high risk for squamous cell carcinoma of the mucocutaneous junctions and for hepatic adenoma. Most of the cancers associated with AT involve the lymphoreticular system, with lymphocytic leukemia and lymphomas being the most common. Individuals with xeroderma pigmentosum are predisposed to develop myriad basal and squamous cell carcinomas. The new chromosome instability syndromes comprise porokeratosis of Mibelli, nevoid basal cell carcinoma syndrome, incontinentia pigmenti, and scleroderma. Porokeratosis is a rare genodermatosis with craterlike lesions surrounded by horny ridges that tend to become malignant. Nevoid basal cell carcinoma syndrome is characterized by multiple basal cell nevi, odontogenic keratocysts, and skeletal anomalies. The most frequent malignancies are basal cell carcinomas; brain tumors and ovarian carcinomas have also been seen. Incontinentia pigmenti is characterized by skin pigmentation anomalies in combination with a variety of malformations. Cancer has been reported in only two affected patients, a 4-mo-old girl with acute myelogenous leukemia and a 14-yr-old girl with pheochromocytoma. Over 25 patients have been reported with scleroderma (progressive systemic sclerosis) and alveolar cell adenocarcinoma of the lung. The new chromosome instability syndromes are inherited differently from the classic ones and are presumably caused by different types of genetic lesions, such as defects in receptor sites or structural proteins. (123 refs.)

77-5439 Monogenic Disorders Associated with Neoplasia. (Eng.) Gorlin, R. J. (Dept. Oral Pathology, Sch. Dentistry, Univ. Minnesota, Minneapolis, MN 55455). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy. 3: 169-178; 1977.

The following seven disorders are discussed in which single gene traits are accompanied by neoplastic manifestations: nevoid basal cell carcinoma syndrome, multiple chemodectomas, multiple hamartoma and neoplasia (Cowden's) syndrome, multiple sebaceous adenomas and gastrointestinal and other carcinomas, cutaneous leiomyoma, hereditary lipomatosis, multiple cutaneous angiolipomas, glomangioma, and blue rubber bleb nevus syndrome. (104 refs.)

77-5440 Malignant Neoplasms in Heterozygous Carriers of Genes for Certain Autosomal Recessive Syndromes. (Eng.) Swift, M. (Dept. Medicine, Biological Sciences Res. Center, Univ. North Carolina, Chapel Hill, NC 27514). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy 3: 209-215; 1977.

A statistical method has been used to analyze cancer incidence in relatives of patients with rare autosomal recessive syndromes. Results show that persons carrying the ataxia-telangiectasia or the Fanconi's anemia gene may constitute 5-10% of all individuals who develop certain neoplasms, 5% of those dying before age 45 from any malignancy, and 3% of those dying from malignancy at any age. (12 refs.)

77-5441 Family Studies: The Interdisciplinary Approach. (Eng.) Blattner, W. A. (Environmental Epidemiology Branch, NCI, Bethesda, MD 20014). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy 3: 269-280; 1977.

An interdisciplinary approach to studying familial cancer applies laboratory techniques to the analysis of environmental and genetic risk factors. Recommendations to clinicians and researchers involve a close search for host and environmental antecedents of familial aggregation, including chromosomal, metabolic, and immune disorders. (52 refs.)

77-5442 Investigative Approach to Familial Cancer: Clinical Studies. (Eng.) Li, F. P. (Clinical Studies Section, Clinical Epidemiology Branch, NCI, and Sidney Farber Cancer Center, Boston, MA 02115). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy 3: 263-268; 1977.

Studies of four families have revealed familial aggregation of soft-tissue sarcomas in association with other neoplasms, particularly breast cancer. A questionnaire has been dev

ped to aid in investigating family history and possible etiologic factors, particularly in patients with cancers that have strong familial tendency. (12 refs.)

7-5443 Relevance of Twin Studies in Cancer Research. (Eng.) Nance, W. E. (Dept. Human Genetics, Medical Coll. Virginia, Richmond, VA 23298). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy 3: 27-41; 1977.

Studies of cancer in twins have provided surprisingly little evidence of the role of inherited differences in cancer development. It is suggested that twin and twin family studies be used for the genetic analysis of quantitative risk factors; especially in the case of identical twins discordant for cancer, twin studies could illuminate the combination of genetic and environmental influences on specific cancers. (31 refs.)

7-5444 Cancer and Congenital Malformations: Another View. (Eng.) Miller, R. W. (Clinical Epidemiology Branch, NCI, Bethesda, MD 20014). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press) Progress in Cancer Research and Therapy 3: 77-81; 1977.

Hospital records of 440 children with Wilms' tumor were examined for collateral disease in the patient or his family. Three cases of congenital hemihypertrophy and six cases of polydactyly were found. Other disorders commonly associated with Wilms' tumor, leukemia and lymphoma are also discussed. (15 refs.)

7-5445 Childhood Tumors and Their Relationship to Birth Defects. (Eng.) Bolande, R. P. (Dept. Pathology, Montreal Children's Hosp., McGill Univ., Montreal, Quebec, Canada). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy, Vol. 3, 519 pp.; 43-75; 1975.

The relationship between teratogenesis and childhood oncogenesis is reviewed. Many tumors manifest at birth or shortly thereafter, such as Wilms' tumor, neuroblastoma, retinoblastoma, sacrococcygeal teratoma, and hepatoblastoma, display surprisingly benign behavior, sometimes despite extremely malignant cellular features. However, a tumor of identical morphologic features in later life usually is highly lethal. This leads to the hypothesis that an oncogenic period of grace exists, beginning in utero and extending through the first

months of postnatal life. Neoplasms seem repressed during this period tending toward benignity through arrested growth, regression, or cytodifferentiation. Wilms' tumor, lymphoreticular malignancies, hepatoblastoma, leukemia, neuroblastoma, retinoblastoma, brain tumors, and testicular-ovarian tumors are all associated with an increase in congenital abnormalities. Specific chromosomal abnormalities are directly related to teratologic syndromes and, in selected instances, are associated with an increased incidence of neoplasms. Many agents known to be carcinogenic postnatally are teratogenic to the fetus or embryo. The frequency of three prenatal events, direct fetal radiation, maternal virus infection, and threatened abortion, is slightly but significantly higher for children dying of cancer than for a comparable group of healthy children. In animal studies using urethane, and the alkyl nitrosoureas, especially ethylnitrosourea, carcinogenesis tended to be max in the latter stages of gestation, occurring only after organogenesis was complete. Prior to this time, teratogenesis was the prevalent response. It appears that the timing of the initiating events may be critical in determining the outcome. The degree of cytodifferentiation and the metabolic or immunologic state of the organism may determine whether the effect is teratogenic and/or oncogenic. (130 refs.)

77-5446 Clonal Origin and Stem Cell Evolution of Human Tumors. (Eng.) Fialkow, P. J. (Medical Service, Veterans Admin. Hosp., Seattle, WA 98108). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy, Vol. 3, 519 pp.; 439-453; 1977.

Studies of the origin and evolution of human tumors using the genetic marker glucose-6-phosphate dehydrogenase (G-6-PD) are reviewed. In eight G-6-PD heterozygotes with Philadelphia chromosome-positive chronic myelocytic leukemia (CML) both G-6-PD A and G-6-PD B (double-enzyme phenotypes) were found in skin fibroblasts, but only a single G-6-PD type was seen in the CML granulocytes. This suggests a clonal origin of CML. Genetic marker studies indicate that the alteration responsible for the development of CML occurs in marrow stem cells, and they support the hypothesis that CML is caused by spontaneous or radiation-induced genetic accidents. It is also suggested that polycythemia vera is a stem cell disorder with a clonal origin. Lymphoproliferative disorders have been studied most extensively with immunoglobulin (Ig) markers. Multiple myeloma, chronic lymphocytic leukemia (CLL) and Waldenstrom's macroglobulinemia appear to be clonal disorders of B lymphocytes. In CLL there is a maturation block in the proliferating clone that is not found in multiple myeloma or Waldenstrom's macroglobulinemia. Results of G-6-PD studies in some hereditary tumors, such as multiple neurofibromatosis and multiple trichoepitheliomas, are compatible with multiple

cell origin. Studies of other hereditary tumors, such as xeroderma pigmentosum, indicate a clonal origin. Although a viral cause (Epstein-Barr virus) is postulated for Burkitt's lymphoma and its clinical presentation suggests multifocal disease, G-6-PD and Ig marker data indicate a clonal origin. Marker studies also indicate that early relapses of Burkitt's lymphoma (< 3 mo after remission) represents reemergence of the original malignant cell lines, but some later recurrences (5 mo) may be the result of new tumor lines. This suggests the existence of factors predisposing to Burkitt's lymphoma. (61 refs.)

- 77-5447 **Tumors of the Neural Crest System.** (Eng.) Schimke, R. N. (Univ. Kansas Medical Center, Coll. Health Sciences and Hosp., Kansas City, KS 66103). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy, Vol. 3, 519 pp.; 179-198; 1977.

Malignant conditions in which the neoplastic tissue is solely derived from the neural crest or in which this structure has been strongly incriminated in the pathogenesis of malignancy are discussed. Heritable neuroblastomas tend to be multifocal, to occur at younger ages than the sporadic lesions, and, in the case of paired organs, to be bilateral. Neuroblastoma is one of the purest examples of malignancy in a derivative of the neural crest system. Multiple instances of two-generation transmission of tumors of the paraganglia or chemodectomas have been described; inheritance of the familial lesion is that of an autosomal dominant disorder. The pigment-producing cell is also derived from the neural crest, indicating that cutaneous melanoma, ocular melanoma, and neurocutaneous melanosis are neurocristopathies. Most of the clinical manifestations of neurofibromatosis or von Recklinghausen's syndrome are related to the neuromas or neurofibromas that anatomically disrupt normal growth and development. The entire syndrome is considered a developmental anomaly of the neural crest. In pheochromocytoma, bilateral and extraadrenal lesions are the rule and true malignant degeneration is rare. Carcinoid tumors have been found at all levels of the gastrointestinal tract and in the tracheobronchial tree, thymus, parotid glands, and gonads. Both the enterochromaffin system and many components of the endocrine system may be derived from the neural crest. The multiple endocrine neoplasia syndromes (Werner's syndrome, Sipple's syndrome, and the mucosal neuroma syndrome) are due to faulty differentiation of the neural crest. Multifocal medullary thyroid carcinoma has been reported in families in the absence of pheochromocytoma, and with and without parathyroid adenomas. Some Turner's syndrome patients harbor nongonadal neoplasias of neural crest origin. Noonan's syndrome has also been associated with tumors of the neural crest, such as schwannoma and pheochromocytoma. (92 refs.)

- 77-5448 **Phacomatoses, Hamartoses, and Neurocristopathies: A Personal View.** (Eng.) Warkany, J. (Children's Hosp. Res. Foundation, Cincinnati, OH 45229). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy 3: 199-204; 1977.

Disorders of heterogeneous origin are nevertheless grouped together as phacomatoses. The hamartoses are uniformly systemic, begin as tissue malformations and are usually transmitted from parent to child in the manner of a dominant trait. New fluorescent methods for identifying neural crest cells during migration may clarify the concept of neurocristopathies. (4 refs.)

- 77-5449 **Cancer of the Pancreas.** (Eng.) Howard, J. M. (Medical Coll. Ohio, Toledo, OH); Jordan, G. L. *Curr Probl Cancer* 2(3): 3-52; 1977.

The incidence, pathology, clinical features, diagnosis, and management of pancreatic cancer are reviewed. For management purposes, it is suggested that pancreatic adenocarcinomas be classified according to whether or not they produce obstructive jaundice. In the US, pancreatic cancer ranks fourth among malignancies as a cause of death. Probable etiologic factors include smoking and exposure to industrial chemicals, such as nitrourethane, acetylaminofluorene, and methylcholanthrene. (51 refs.)

- 77-5450 **Glycoprotein Alteration in Human Colonic Adenocarcinoma.** (Eng.) Kim, Y. S. (Gastrointestinal Res. Lab., Univ. California Veterans Admin. Hosp., 4150 Clement St., San Francisco, CA 94121). *Adv Exp Biol Med* 89: 443-468; 1977.

Studies of blood group activity, lectin reactivity, and hydrocarbon composition of the membrane glycoproteins of normal human colonic mucosa and colonic adenocarcinomas are reviewed. Glycoproteins containing blood group A activity were markedly decreased in the cancer tissues. This change was associated with a reduction of the enzyme responsible for the biosynthesis of A antigen and with a decrease in the concentration of N-acetylgalactosamine. Glycosidase activities were unchanged. The tumor tissues also exhibited a decrease in sugar content, alterations in other antigens, and changes in the levels of several glycosyltransferases. Whether alterations in glycoprotein biosynthesis are primary events or are secondary to neoplastic transformation remains to be determined. (33 refs.)

- 77-5451 **Derangements of Biosynthesis, Production and Secretion of Mucus in Gastrointestinal Injury and Disease.** (Eng) Glass, G. B. (Gastroenterology Res. Lab., Dept. Medicine, New York Medical Coll., New York, NY 10029); Slomiany, B. L. *Adv Exp Med Biol* 89: 311-349; 1977.

The effects of anti-inflammatory drugs (phenylbutazone, aspirin, indomethacin, and corticosteroids), alcohol, stress, and gastrointestinal disease on mucus production and secretion in the gastrointestinal mucosa are reviewed. The effects considered are quantitative and qualitative changes in mucus, increased shedding of the mucus-containing surface epithelial cells and excessive extrusion of cell mucus, and abnormalities in mucus glycoprotein synthesis. Derangements in mucus production and glycoprotein synthesis are described for ulcerative colitis, Crohn's disease, celiac disease, cystic fibrosis, Whipple's disease, and gastrointestinal cancer. The presence of tumor-specific antigens in human gastrointestinal cancer is considered. (170 refs.)

- 77-5452 **The Biochemical Pharmacology of Mucus.** (Eng) Parke, D. V. (Univ. Surrey, Dept. Biochemistry, Guildford, Surrey, England); Symons, A. M. *Adv Exp Med Biol* 89: 423-441; 1977.

The pharmacology of agents that affect the mucus of the respiratory tract, endometrium, cervix, and gastrointestinal tract is discussed. Special attention is given to the effects of carbenoxolone on the incorporation of labeled N-acetylglucosamine into gastric mucosal glycoproteins, on the incorporation rates of labeled sugar moieties into mucosal glycoproteins, and on the carbohydrate components and enzymes of the gastrointestinal tract. In addition to stimulating glycoprotein synthesis, carbenoxolone inhibits DNA synthesis in murine gastric epithelial cells, has a marked cytostatic effect on cultured malignant tumors, and protects the rough endoplasmic reticulum against degranulation by chemical carcinogens. (40 refs.)

- 77-5453 **Dynamic Anatomy of the Cervical Epithelium.** (Eng) Singer, A. (Dept. Obstetrics and Gynecology, Univ. Sheffield Jessop Hosp. Women, Sheffield, S3 7RE, England). *Adv Exp Med Biol* 89: 77-89; 1977.

The development of human cervicovaginal epithelium, the morphology of the cervical epithelium, and the cervical anatomy of mucus secretions are discussed. The cervical surface epithelium changes at many periods during life. These changes are principally due to the occurrence of metaplastic squamous epithelium within the transformation zone. The process dramatically influences cervical mucus secretion, and it appears to hold the key to an understanding of the origin of neoplastic development in the cervix. (21 refs.)

- 77-5454 **Endocrine Function and Breast Cancer.** (Eng.) Henderson, B. E. (Univ. Southern California Sch. Medicine, Los Angeles, CA 90033); Gerkins, V. R.; Pike, M. C.; Casagrande, J. T. *In: Genetics of Human Cancer.* Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy 3: 291-295; 1977.

Studies were conducted in an attempt to amalgamate the familial risk of breast cancer with a variety of hormonal interactions. Familial risk seemed at least partly associated with risk factors common to the patient and her first degree relatives, suggesting that endocrinopathology associated with breast cancer could be inherited. (38 refs.)

- 77-5455 **Genetic Cerumen Type, Breast Secretory Activity, and Breast Cancer Epidemiology.** (Eng.) Petrakis, N. L. (G. W. Hopper Foundation and Dept. International Health, Univ. California Sch. Medicine, San Francisco, CA 94143). *In: Genetics of Human Cancer.* Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy 3: 297-300; 1977.

A working model is described based on the known epidemiologic evidence of the association between factors in reproductive experience and the risk of breast cancer in Caucasian and Oriental women. The lower risk in Oriental women may be due to their overall decrease in breast secretory activity, especially marked in those with genetically dry-type apocrine systems. (16 refs.)

- 77-5456 **Genetics of Human Cancer: An Epidemiologist's View.** (Eng.) Miller, R. W. (Clinical Epidemiology Branch, NCI, Bethesda, MD 20014). *In: Genetics of Human Cancer.* Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F. (New York: Raven Press): Progress in Cancer Research and Therapy. 3: 481-482; 1977.

Because physicians traditionally concentrate on diagnosis and therapy, rather than on the causes of disease, it is suggested that each medical school have a clinical etiologist on its staff. (no refs.)

- 77-5457 **Current Studies in the Epidemiology of Cancer: Questions and Answers.** (Eng) Kessler, I. (NCI Conference on Cancer Epidemiology and the Clinician, Boston, MA); Evans, A.; Smith, P. G. *Cancer [Suppl]* 39(4): 1909-1911; 1977.

The current status of epidemiology in establishing causes of cancer is reviewed. Particular attention is focused on marriage and the risk of cervical cancer, Epstein-Barr virus and Burkitt's tumor, malaria and Burkitt's tumor, and mammography in breast cancer screening. (no refs.)

- 77-5458 Ethnic Differences in Cancer Occurrence: Genetic and Environmental Influences with Particular Reference to Neuroblastoma.** (Eng.) Miller, R. W. (Clinical Epidemiology Branch, NCI, Bethesda, MD 20014). In: *Genetics of Human Cancer*. Mulvihill, J. J.; Miller, R. W.; Fraumeni, J. F.; eds. (New York: Raven Press): Progress in Cancer Research and Therapy, Vol. 3, 519 pp.; 1-14; 1977.

Ethnic differences in cancer occurrence are reviewed for blacks, Arabs, Chinese, and Japanese, and international variations in certain childhood cancers are considered in relation to the two-mutation hypothesis of the development of retinoblastoma. Ewing's tumor and testicular cancer are virtually nonexistent in blacks in both the US and Africa, suggesting genetic resistance to these neoplasias. Multiple myeloma affects substantially more US blacks than whites and may be due to a genetic influence on immune status. Blacks of all ages have higher levels of the three major immunoglobulins than whites. Acute lymphocytic leukemia, which has been much more prevalent among white children than black, is apparently partly due to environmental factors. Black children are either not exposed or not susceptible. In the case of melanoma, a genetically determined racial trait, dermal pigmentation, protects against an environmental carcinogen, actinic radiation. There is a high prevalence of xeroderma pigmentosum among Arabs. In this instance, a racial predisposition to cancer is caused by a particular autosomal recessive trait that has accumulated in this group. Other examples include Bloom's syndrome among Jews who are at high risk of leukemia, and ataxia-telangiectasia among Moroccan Jews in Israel who are predisposed to lymphoma and acute lymphocytic leukemia. Studies on the low rate of breast cancer in Japan indicate that what appeared to be a genetically determined ethnic difference in occurrence is, in fact, environmentally mediated. The two-mutation hypothesis of tumorigenesis states that two events are involved in the development of retinoblastoma: a prezygotic mutation plus a postzygotic mutation in heritable cases and two postzygotic mutations in sporadic cases. (53 refs.)

- 77-5459 The Epidemiology of Oral Cavity, Pharyngeal and Esophageal Cancer Outside of North America and Western Europe.** (Eng.) Mahboubi, E. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB 68105). *Cancer [Suppl]* 40(4): 1879-1886; 1976.

Geographical variations in the incidence of oral cavity, pharyngeal, and esophageal cancer were studied, with special reference to the rates in Africa, Asia, Eastern Europe, and South America. Although reporting techniques differ greatly and comparisons must be made with caution, significant variations are evident. The roles of known environmental carcinogens, such as *N*-nitroso compounds and polycyclic aromatic hydrocarbons, and of cultural habits, such as smoking or chewing tobacco and excessive consumption of alcoholic beverages, in the etiology of these cancers are discussed. (45 refs.)

- 77-5460 Role of Diet in Cancer Etiology.** (Eng.) Modan, B. (Dept. Clinical Epidemiology, Chaim Sheba Medical Center, Tel Hashomer, Israel). *Cancer [Suppl]* 40(4): 1887-1891; 1977.

Indirect relationships between the consumption of selected food constituents and incidence, dietary studies, and laboratory data are the bases for current evidence on the involvement of diet in cancer etiology. The indirect evidence most often referred to is the suggested correlation between the fat-meat-egg-animal protein complex and the risk for colon cancer. However, these observations are hampered by the fact that human diet does not consist of isolated food components. Case control studies implicate a higher intake of starchy foods in gastric cancer, a lower intake of fiber in colon cancer, and, possibly, coffee in renal cancer. Carcinogenic agents identified include food additives, plant toxicants, aflatoxins, polycyclic hydrocarbons, nitrosamines, and certain normal major food constituents. The experimental evidence is augmented by studies indicating an interrelationship between dietary constituents, intestinal flora, and bile acid metabolism. A synergistic action of ingested or metabolized carcinogens and cocarcinogenic function of certain dietary components are suggested. (62 refs.)

- 77-5461 Essential Fatty Acids: What Level in the Diet Is Most Desirable?** (Eng.) Carroll, K. K. (Dept. Biochemistry, Univ. Western Ontario, London, Ontario, Canada N6A 5C1). *Adv Exp Med Biol* 83: 535-546; 1977.

The possibility that high dietary levels of polyunsaturated fats (15%-20% of total calories as linoleic acid) may promote gallstone formation and the development of breast and intestinal cancer is discussed. Data from animal experiments and clinical trials on humans are reviewed. Adults at high risk of coronary heart disease may be justified in increasing their intake of essential fatty acids to 15% of their total calories, but for the general population, 5% appears to be more than adequate. (63 refs.)

CHEMICAL CARCINOGENESIS

77-5462 **Carcinogenic Activity of 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide, a Food Additive, in Mice and Rats.** (Eng.) Takayama, S. (Dept. Experimental Pathology, Cancer Inst., 1-37-1 Kami-Ikebukuro, Toshimaku, Tokyo, Japan); Kuwabara, N. *Cancer Lett* 3(3/4): 115-120; 1977.

The effects of po administration of two dose levels of 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2) to Wistar rats and CDF mice for 18 mo were studied. Each species was divided into three groups of 100 animals each (50 males, 50 females): Group 1 was given 0.4% AF-2 in the diet, Group 2 0.08% AF-2, and Group 3 basal diet only. AF-2 induced malignant tumors in both species and muscle atrophy in the male rats. In the Wistar rats, most of the tumors were found in the mammary gland and forestomach. The first appeared 9 mo after the start of treatment. Mammary tumors originated from either the glandular or excretory epithelium, and most were adenocarcinomas. Among 82 effective mice treated with AF-2, 32 had papillomas and 20 had squamous cell carcinomas of the forestomach (observed in the 11th mo). Eight of 20 mice with squamous cell carcinomas had metastases to the liver, lung, peritoneal cavity, and regional lymph nodes. The results show that AF-2 is carcinogenic to rats and mice. (12 refs.)

77-5463 **Enzyme-Catalyzed Reaction of AF 2 with DNA In Vitro.** (Eng.) Tanaka, N. (Dept. Chemistry, Gakushuin Univ., Tokyo, 171 Japan); Sugiura, K.; Hattori, M.; Goto, M. *Chemosphere* 6(9): 569-573; 1977.

In the presence of mouse liver microsome enzymes, furylfuramide (AF 2) was metabolized to an active intermediate that inhibited the growth of wild and recombination-deficient (Rec-) strains of *Bacillus subtilis*. However, the growth inhibitory effect of AF 2 on the Rec- strains diminished when the compound was metabolized completely. The binding of AF 2 to DNA required the presence of microsomes and coenzyme systems, and the level of binding was one AF 2 molecule per 2,000-4,000 nucleotides. The enzyme-catalyzed binding of AF 2 to DNA is presumably the cause of its mutagenicity. (17 refs.)

77-5464 **Cryofracture of Transitional Epithelium after Treatment with the Carcinogen FANFT (Meeting Abstract).** (Fre) Thiele, J. (Insitut de Pathologie, Ecole de Medecine, 3 Hannover, W. Germany); Adolphs, H. D.; Reale, E. *Biol Cellulaire* 29(1): 16a; 1977. (no refs.)

77-5465 **O-Sulfonation of N-Hydroxy-2-fluorenylacetamide and 7-Hydroxy-N-2-fluorenylacetamide in Fetal and Placental Tissues of Humans and Guinea Pigs.** (Eng) Namkung, M. J. (Dept. Pharmacology, Sch. Medicine, SJ-30 Univ. Washington, Seattle, WA 98195); Zachariah, P. K.; Juchau, M. R. *Drug Metabol Dispos* 5(3): 288-294; 1977.

By incubating 0.2-3.0 mg of the soluble 104,000-g supernatant protein obtained from homogenized primate tissues with 5 mg transfer RNA and 0.1 micromole (μ mol) of N-hydroxy-2-fluorenylacetamide (N-OH-FAA) in the presence of 20 μ mol Na_2SO_4 , 5 μ mol ATP, and 8 μ mol MgCl_2 , O-sulfonation of the N-hydroxyarylamide in various fetal and adult tissues could be measured. O-Sulfonation and other esterifying reactions involving N-OH-FAA in human and monkey fetal tissues were less active than those observed in rat liver (susceptible to tumorigenic action), but more active than those of the adult guinea pig liver (resistant to tumorigenic action). Sulfonation of 7-hydroxy-N-2-fluorenylacetamide (7-OH-FAA), β -estradiol, and other xenobiotic phenolic substrates occurred rapidly in incubation flasks containing human fetal lung, liver, or kidney as the enzyme source. The specific activities in these tissues were 10-100 times higher than those in adult monkey liver and similar to those in maternal guinea pig liver. The results indicate that human fetal and placental tissues possess all the requisite enzymes for bioactivation of N-2-fluorenylacetamide via N-oxygenation and subsequent N-O esterification. (27 refs.)

77-5466 **The Effects of a Marginally Lipotrope-deficient Diet on the Hepatic Levels of S-Adenosylmethionine and on the Urinary Metabolites of 2-Acetylaminofluorene in Rats.** (Eng) Poirier, L. A. (Carcinogen Metabolism and Toxicology Branch, NCI, NIH, Bethesda, MD 20014); Grantham, P. H.; Rogers, A. E. *Cancer Res* 37(3): 744-748; 1977.

Hepatic levels of S-adenosylmethionine (AdoMet), glutathione, and the microsomal enzymes p-nitroanisole demethylase and benzo(a)pyrene hydroxylase (BPOH) were measured in male and female Sprague-Dawley rats fed a diet marginally deficient in choline and methionine and void of folic acid (lipotrope-deficient) or an adequate diet for 0-14 wk with and without added 2-acetylaminofluorene (AAF). Urinary AAF metabolites were determined throughout the experiment. After 2-4 wk, hepatic AdoMet levels were 43% lower in male rats fed the lipotrope-deficient diet than in male rats fed the lipotrope-adequate diet. No differences were found in the

hepatic AdoMet levels of females fed either diet for 2-14 wk. Administration of AAF to lipotrope-deficient female rats for 2 wk led to a transient decrease in AdoMet hepatic levels. The administration of AAF for 2-14 wk did not significantly affect hepatic AdoMet in females fed the lipotrope-adequate diet or in males fed either diet. Females fed the lipotrope-deficient diet and treated with AAF excreted decreased proportions of N-hydroxy-2-acetylaminofluorene (N-hydroxy-AAF) and increased proportions of 5-hydroxy-2-acetylaminofluorene (5-hydroxy-AAF) in their urine. However, the urine of lipotrope-deficient males treated with AAF contained increased proportions of N-hydroxy-AAF and decreased levels of 5-hydroxy-AAF. The urinary excretion of 7-hydroxy-AAF by male and female lipotrope-deficient rats treated with AAF was generally similar to that in lipotrope-adequate rats. The lipotrope-deficient diet did not appear to alter the hepatic levels of glutathione, p-nitroanisole demethylase, or BPOH in male or female rats. BPOH activity was lower in the livers of lipotrope-deficient male rats treated with AAF for 8-14 wk than in the livers of lipotrope-deficient rats not receiving the carcinogen. The altered metabolism of AAF correlated well with previously reported effects of marginal lipotrope deficiency on AAF carcinogenesis. (26 refs.)

- 77-5467 **Increased Urinary Excretion of 1-Methyl-2-pyridone-5-carboxamide in Rats Administered 2-Acetylaminofluorene.** (Eng.) Ohkubo, M. (Div. Biochemistry, Chiba Cancer Center Res. Inst., Chiba 280, Japan) Shimizu, M.; Kubo, A.; Fujimura, S. *Chem Biol Interact* 18(1): 101-110; 1977.

During the dietary administration of the hepatocarcinogen, 2-acetylaminofluorene (AAF, 0.05%) to Wistar male rats, the urinary excretion of 1-methyl-2-pyridone-5-carboxamide (2-PY) gradually increased. A plateau was reached at 21 wk that was maintained even after treatment was terminated at 20 wk. The excretion of 1-methyl-4-pyridone-5-carboxamide (4-PY) decreased. All the urinary radioactivity 0-9 hr after ip injection of 1-[methyl- ^{14}C]methyl nicotinamide (1-CH₃Nmd) at week 20 was recovered as pyridones. Only 4-PY was labeled in control rats but both pyridones were labeled almost equally in the AAF-treated rats. The specific activity of 2-PY formation by 1-methylnicotinamide oxidase (1-CH₃Nmd oxidase) of AAF-treated rat liver during weeks 16-30 was three times higher than that of the control rat liver, but 4-PY-forming enzyme activity decreased to around 20% of the control value. In control rat liver, 4-PY-forming activity showed a max at pH 9.0, but 2-PY-forming activity continued to increase with increasing pH. However, in AAF-treated rat liver both 2-PY- and 4-PY-forming activities increased as pH increased. Km values for 1-CH₃Nmd of the 2-PY- and 4-PY-forming enzyme in control rat liver were 4.22×10^{-4} and 6.4×10^{-5} M, respectively, and in AAF-treated rat liver they were 4.63×10^{-4} and 5.03×10^{-4} M, respectively. (20 refs.)

- 77-5468 **Differential Excision from DNA of the C-8 and N² Guanosine Adducts of N-Acetyl-2-aminofluorene by Single Strand-specific Endonucleases.** (Eng) Yamasaki, H. (Inst. Cancer Res., Columbia Univ., Coll. Physicians and Surgeons, New York, NY 10032); Pulkarabek, P.; Grunberger, D.; Weinstein, I. B. *Cancer Res* 37(10): 3756-3760; 1977.

Purified duck reticulocyte DNA was reacted in vitro with [9- ^{14}C] N-acetoxy-N-acetyl-2-aminofluorene. Hydrolysis of the [^{14}C] N-acetyl-2-aminofluorene (^{14}C -AAF)-modified DNA followed by Sephadex LH-20 column chromatography showed that 85% of the DNA-bound ^{14}C -AAF was N-(deoxyguanosin-8-yl)-N-acetyl-2-aminofluorene [N-(deoxyguanosin-8-yl)-AAF] and 15% was 3-(deoxyguanosin-N²-yl)-N-acetyl-2-aminofluorene [3-(deoxyguanosin-N²-yl)-AAF]. When this modified DNA was incubated with the single-strand specific nuclease S₁ and the undigested fraction of the DNA was analyzed, there was preferential loss of the guanosine C-8 adduct from the DNA. Moreover, analysis of the nucleosides released by exposure of AAF-modified DNA to a single-strand specific nuclease from *Neurospora crassa* showed only the guanosine C-8 adduct in the supernatant fraction. The results suggest that although the [N-(deoxyguanosin-8-yl)-AAF] adduct in DNA causes major conformational changes in the double-stranded helix and localized regions of denaturation, the [3-(deoxyguanosin-N²-yl)-AAF] adduct does not cause major distortions of the native DNA structure. (23 refs.)

- 77-5469 **Studies on Metabolism of 2-Acetylaminofluorene by Rat Liver Cells in Replicating Monolayers (Meeting Abstract).** (Eng) Lallemand, C. (Laboratoire de Cytogenetique, Faculte de Medicine, 7, bd Jeanne d'Arc, 21033 Dijon, France); Chessebeuf, M.; Exilie, M. F.; Wood, G.; Padieu, P. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 79; 1977. (no refs.)

- 77-5470 **Conversion of the Carcinogen N-Acetoxy-2-acetamidofluorene to 4-Hydroxy-2-acetamidofluorene (Letter to Editor).** (Eng) Scribner, J. D. (Pacific Northwest Res. Foundation, Seattle, WA 98104). *J Am Chem Soc* 99(22): 7383-7384; 1977.

An unusual reaction involving water and N-acetoxy-2-acetamidofluorene is reported that results in conversion of the latter to 4-hydroxy-2-acetamidofluorene [N-(4-hydroxy-2-fluorenyl)acetamide]. It is suggested that hydroxylation of the intermediate N-acetyl-N-fluorenylnitrenium is followed by further hydration of the ensuing quinone imide methide

and dehydration of the resulting diol. Steric accessibility is not a factor. A previous analysis of this reaction resulted in an inappropriate chromatographic identification of the end product as 1-acetoxy-2-acetamidofluorene. This finding negates most of the hypotheses of the role of N-acetoxyacetamidofluorenes in mammary gland carcinogenesis by the corresponding hydroxamic acids. (9 refs.)

7-5471 **Subnanogram Estimation of the Proximate Carcinogen N-Hydroxy-2-fluorenylacetamide by Gas-Liquid Chromatography.** (Eng) Razzouk, C. (Lab. Biotoxicologie, CMTB, Univ. Louvain, Pharmacy Sch., U.C.L. 369 B. 1200 Bruxelles, Belgium); Lhoest, G.; Roberfroid, F.; Mercier, M. *Anal Biochem* 83(1): 194-203; 1977.

A procedure using gas-liquid chromatography with electron-capture detection for determination of as little as 0.05 nanogram quantities of N-hydroxy-2-fluorenylacetamide is described. The method is rapid and sensitive and can be applied to every N-hydroxy derivative. (18 refs.)

7-5472 **Hepatic Microsomal N-Glucuronidation and Nucleic Acid Binding of N-Hydroxy Arylamines in Relation to Urinary Bladder Carcinogenesis.** (Eng) Kadlubar, F. F. (Natl. Center Toxicological Res., Jefferson, AR 72079); Miller, J. A.; Miller, E. C. *Cancer Res* 37(3): 805-814; 1977.

The uridine 5'-diphosphoglucuronic acid (UDPGA)-dependent enzymatic glucuronidation of the N-hydroxy derivatives of 1-naphthylamine (1-NA) and 2-naphthylamine (2-NA), 4-aminobiphenyl (4-ABP), 2-aminofluorene (2-AF), 4-aminoazobenzene (4-AAB), and N-acetyl-2-aminofluorene (AAF) by liver microsomes was investigated. UDPGA-fortified hepatic microsomes from the three species metabolized ³H-N-hydroxy-2-NA (N-HO-2-NA) to a water-soluble product that yielded 98% of the parent N-hydroxyamine upon treatment with β -glucuronidase. The metabolite was identified as N-(β -1-glucosiduronyl)-N-hydroxy-2-naphthylamine. Incubation of N-hydroxy-1-NA (N-HO-1-NA), N-hydroxy-4-ABP (N-HO-ABP), or the N-hydroxy derivatives of 2-AF, 4-AAB, or AAF with UDPGA-fortified hepatic microsomes also yielded water-soluble products. β -Glucuronidase treatment released 80% to 90% of the labeled N-HO-1-NA and N-HO-ABP conjugates as labeled ether-extractable derivatives. N-HO-1-NA, N-HO-2-NA, and N-HO-ABP and their glucuronides were relatively stable and nonreactive near neutral pH. At pH 5, the N-glucuronide of N-HO-2-NA and the presumed N-glucuronides of N-HO-1-NA and N-HO-ABP were rapidly hydrolyzed to N-hydroxyarylamines that were then converted to reactive derivatives that could bind to DNA. Thus, it is conceivable that arylamine bladder carcinogens are N-oxidized and N-

glucuronidated in the liver and that the glucuronides are transported to the urinary bladder. There they could be hydrolyzed to N-hydroxyarylamines and converted to electrophilic arylnitrenium ions in the acidic urine, critical reactions for the induction of bladder cancer. (59 refs.)

77-5473 **Properties of the Ames Salmonella Mutants Lodged in the Gastrointestinal Tract of Gnotobiotic Rats.** (Eng) Goldman, P. (Dept. Pathology, Harvard Medical Sch., Boston, MA 02215); Wheeler, L. A.; Carter, J. H.; Ingelfinger, J. A.; Soderberg, F. B. *Am J Clin Nutr* 30(11): 1921-1926; 1977.

The histidine auxotroph of *Salmonella typhimurium* (strain TA1538) was maintained within the gastrointestinal tract of otherwise germ-free Sprague-Dawley rats for up to 7 mo. The bacterial concentrations exceeded 10^7 /g in the forestomach and 10^8 /g in the lower bowel and feces. When the carcinogens 3,2'-dimethyl-4-aminobiphenyl, 2-nitrofluorene, 2-acetylaminofluorene, azoxymethane, and 4-nitrobiphenyl were ingested, the number of revertants in the feces increased. The ingestion of structurally related compounds, which are not mutagenic to the bacteria in vitro and for which no evidence of carcinogenicity exists, did not increase the number of revertants in the feces. The numbers of salmonella increased in the presence of *Lactobacillus plantarum* and *Bacteroides fragilis*, but the salmonella disappeared from the gastrointestinal tract when the rats were returned to normal. With the additional flora, there was a decrease in the number of revertants in the feces in response to a given dose of carcinogen. This decrease may reflect an effect of the flora on the activity of the metabolic pathway responsible for the presence of the ultimate carcinogen or it may simply be an effect on the salmonella mutants themselves. (6 refs.)

77-5474 **A Comparison of the Effects of the Hypocholesteremic Agents, Cholestyramine and Candicidin, on the Induction of Intestinal Tumors in Rats by Azoxymethane.** (Eng.) Nigro, N. D. (Dept. Surgery, Wayne State Univ. Sch. Medicine, Detroit, MI 48104); Campbell, R. L.; Gantt, J. S.; Lin, Y. N.; Singh, D. V. *Cancer Res* 3(9): 3198-3203; 1977.

The effects of ingestion of cholestyramine (Ch: 2% in Purina rat chow) and candicidin (Ca: 0.4%) on intestinal tumor frequency induced by azoxymethane (AOM) in Sprague-Dawley rats were studied. The sc injection of AOM (8 mg/kg/wk) was begun after the animals were fed the specified doses of Ch and Ca for 1 wk and continued for 25 wk. Ch and Ca increased intestinal tumor frequency from an average of five tumors per rat in controls (Ch- and Ca-untreated) to 7.5 in the treated groups. There were no tumors in rats not inoculated with AOM. Ch-treated rats had the same number of

tumors in the small intestine as the control group, but there was a greater number of tumors in the large intestine. In contrast, the Ca-treated animals had a marked increase in small intestinal tumors. The feces of the Ch-treated animals contained more total bile acids and secondary bile acids than normal animals. Feces of the Ca-treated group had increased amounts of cholesterol and a higher degree of cholesterol degradation. Thus, bile acids promote tumorigenesis to a greater extent in the large intestine, but cholesterol and/or its degradation products have a greater tumorigenic effect in the small intestine. Carcinogenesis varies in different parts of the intestinal tract. (23 refs.)

- 77-5475 Tumor Induction in Intact and Regenerating Liver of Adult Rats by a Single Treatment with Methylazoxymethanol Acetate.** (Eng.) Zedeck, M. S. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Sternberg, S. S. *Chem Biol Interact* 17: 291-296; 1977.

A study was made of the incidence of neoplastic nodules and of hepatocellular carcinomas in control and partially hepatectomized adult male Sprague-Dawley rats treated ip with 20-35 mg/kg of methylazoxymethanol acetate (MAMA). Tumors developed after 10 mo in each group. The incidence of neoplastic nodules and of hepatocellular carcinomas was approx 70% in MAMA-treated intact adult rats and around 80% in partially hepatectomized MAMA-treated rats. It is concluded that both dividing and resting liver cells are sensitive to the tumor-initiating effects of MAMA. (23 refs.)

- 77-5476 Breath-Methane in Patients with Cancer of the Large Bowel.** (Eng.) Haines, A. (M.R.C./D.H.S.S. Epidemiology and Medical Care Unit, Northwick Park Hosp., Harrow, Middlesex, England); Dilawari, J.; Metz, G.; Blendis, L.; Wiggins, H. *Lancet* 2(8036): 481-483; 1977.

Cancer of the large bowel may be caused by cocarcinogens formed as a result of the nuclear dehydrogenation of bile acids in the large intestine by anaerobic bacteria. This study was undertaken to determine if there is a correlation between breath methane, produced by the highly anaerobic methanobacteria in the large bowel, and cancer of the large bowel. In 30 patients with cancer of the large bowel, 24 had detectable levels of methane in their breath, compared with 25/64 patients with nonmalignant large bowel disease and 83/208 subjects without large bowel disease. (7 refs.)

- 77-5477 Metabolism of Triphenylmethane Colours. II. Absorption, Excretion and Distribution of Ben-**

zyl Violet 4B (FD and C Violet No. 1) in Rats. (Eng.) Minegishi, K. (Dept. Medical Chemistry, Natl. Inst. Hygienic Sciences, Kamiyoga, Setagaya, Tokyo, Japan) *Yamashita, T. Toxicology* 7(3): 367-383; 1977.

Male and female Wistar and Sprague-Dawley rats were given the carcinogenic dye Benzyl Violet 4B, and its absorption, excretion, and distribution were measured by double-wavelength photometry. When the dye was given to rats po (5 mg/kg), only 0.89% was excreted through the bile after 24 hr. However, when given iv (5 mg/kg), total recovery of biliary excretion was 95.9% at 24 hr. Levels found in the liver, kidney, abdominal muscle, and serum of rats maintained on a diet of 5% Benzyl Violet 4B for 8 wk were in the range of 1-3 µg/g of tissue, whereas rats fed for 18 wk showed decreased levels. Although tumor development has been reported for a high percentage of female Sprague-Dawley rats, no sex-related difference in dye distribution was observed in both strains of rats receiving a single iv dose of 73.4 mg/kg. However, disappearance of the dye from the liver, abdominal muscle, brain, abdominal skin, and ear was slower in Sprague-Dawley rats than in Wistar rats. The dye tended to accumulate more in the external regions, such as the abdominal skin and ear, than in the abdominal muscle. (11 refs.)

- 77-5478 Carcinogen-Protein Antigens and Carcinogenic Activity of Aniline Dyes.** (Rus.) Korosteleva, T. A. (Lab. Immunology to Carcinogenesis, N. N. Petrov Scientific Res. Inst. Oncology, Leningrad, USSR); Skachkov, A. P.; Kondrat'eva, A. F. *Vopr Onkol* 23(7): 72-73; 1977.

Treatment of rats with an aniline dye containing benzidine (Direct Violet C100%) resulted in cleavage of the benzidine during metabolism and its association with hapten. In most animals this association was detectable in the liver and kidney after 4 days. Benzidine-hapten appeared in the blood serum and spleen on the 30th day. When administered to other rats in a daily dose of 500 mg po, Direct Violet C100% induced tumors in 10/18 animals that survived 500 days. The tumors included 4 microcholangiomas, 3 leukemias, 2 plasmacytomas, and 1 renal cell carcinoma. The findings indicate a correlation between the carcinogenicity of a compound and its ability to form antigens containing a carcinogenic group in vivo. (3 refs.)

- 77-5479 Demonstration of Mutagenicity of Aniline and o-Toluidine by Norharman.** (Eng.) Nagao, M. (Natl. Cancer Center Res. Inst., 5-1-1, Tsukiji, Chuo-ku, Tokyo 104, Japan); Yahagi, T.; Honda, M.; Seino, Y.; Matsu-shima, T.; Sugimura, T. *Proc Jpn Acad [B]* 53(1): 34-37; 1977.

The effects of norharman on the mutagenicity of aniline and

p-, m-, and p-toluidine were studied. Aniline alone had no mutagenic activity. In the presence of norharman (200 μ g) and an S-9 mix prepared from the livers of rats treated with polychlorinated biphenyl, it was mutagenic for a frameshift mutant (TA98) of *Salmonella typhimurium*. Norharman (40-100 μ g) and the S-9 mix also potentiated the mutagenicity of p-toluidine, but they had no effect on the activity of the other two phenylamines. The possible mechanisms of the mutagenic activity of norharman are discussed. (10 refs.)

77-5480 **Effect of Selenium on Azo Dye Hepatocarcinogenesis.** (Eng.) Griffin, A. C. (Dept. Biochemistry, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Jacobs, M. M. *Cancer Lett* 3(3-4): 177-181; 1977.

Experiments were conducted to determine whether simultaneous administration of 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB), and selenium to male Sprague-Dawley rats would reduce the incidence of hepatic tumors. Groups of 15 rats were maintained on three regimens: (I) basal diet plus 0.05% 3'-MeDAB, (II) same as plus 6 ppm Se (Na_2SeO_3) in the drinking water, and (III) same as I plus 6 ppm Se in the diet in the form of yeast containing 118 μ g Se/g. After 8 wk, 3'-MeDAB was removed, and the animals were maintained on their respective diets for an additional 4 wk (Se supplements in Groups II and III were continued). At sacrifice, the hepatic tumor incidence was ascertained as the ratio of animals with tumors per total number of survivors per group. Se reduced the tumor incidence from 11/12 in Group I, (3 animals died early in the study) to 7/15 in Group II and 9/14 in Group III. (10 refs.)

77-5481 **Molecular Composition of Lecithins in the Primary Hepatoma Induced by 3'-Methyl-4-dimethylaminoazobenzene.** (Eng.) Okano, G. (First Div., Dept. Biochemistry, Cancer Res. Inst., Sapporo Medical Coll., Sapporo, Japan); Akino, T.; Mochizuki, Y. *Tohoku J Exp Med* 122(1): 21-33; 1977.

The molecular structure of lecithin in a primary hepatoma induced by 3'-methyl-4-dimethylaminoazobenzene (DAB) in male Wistar rats was investigated. The majority of the lecithin in the hepatoma was a diacyl type; therefore the low amounts of alkenyl-acyl and alkyl-acyl lecithins were not removed before further analysis. The fatty acid composition was similar to that in preneoplastic hyperplastic nodules. Most of the saturated acids were in position 1, while the unsaturated acids selectively occupied position 2. The fatty acid composition remained similar through different stages of malignancy and was consistent with previous findings. Hepatoma unsaturated-unsaturated species were similar as compared to host liver lecithins, while the saturated-

unsaturated type was decreased and the saturated-saturated and unsaturated-saturated increased. DAB hepatoma lecithins were different from those previously reported for transplanted hepatomas. The formation of unusual lecithin species in tumor tissues is discussed in relation to enzyme impairment. (35 refs.)

77-5482 **Antigenic Rearrangement in the Livers of Mice and Rats as a Result of a Single Carcinogenic Treatment.** (Rus.) Ivanov, V. A. (Lab. Tumor Cell Genetics, Inst. Cytology, Acad. Sciences USSR, Leningrad, USSR); Avertsev, S. A.; Fel', V. Ia.; Olenov, Iu. M. *Tsitologiya* 19(7): 781-785; 1977.

The effects of single ip doses of 4-dimethylaminoazobenzene (DAB: 50 mg), dimethylnitrosamine (DMNA: 6 mg), and aminoazotoluene (AAT: 20 mg) on water-soluble and insoluble liver antigens were studied in randomly bred male rats and in C3HA male mice by immunodiffusion and agar precipitation. Although at least five soluble organ-specific antigens were found in the livers of untreated animals, not more than two antigens were detectable 1-4 days after the administration of DAB or DMNA. However, there was no difference between DAB- or DMNA-treated and untreated animals after 11 days. Kidney cell membrane antigens were found on hepatocyte membranes 1-18 days after the administration of DAB or DMNA. Soluble hetero-organic antigens characteristic of 22a hepatoma cells were found in the liver for up to 2 mo after AAT. The findings indicate that the synthesis of organospecific antigen is inhibited and the synthesis of heteroorganic antigens is stimulated by single doses of DAB, DMNA, and AAT. (10 refs.)

77-5483 **Carcinogenic Activity of Hexachlorobenzene in Hamsters.** (Eng.) Cabral, J. R. (Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NB 68105); Shubik, P.; Mollner, T.; Raitano, F. *Nature* 269(5628): 510-511; 1977.

The carcinogenicity of hexachlorobenzene (HCB) was evaluated in 6-wk-old Syrian golden hamsters fed HCB at concentrations ranging up to 200 ppm. There was a significant induction of hepatomas, hemangiomas and thyroid adenomas in these animals; tumor occurrence was dose-related. It is not possible to extrapolate these results to man. (8 refs.)

77-5484 **Reductive Dechlorination of Chlorobiphenyls by Rats.** (Eng.) Tulp, M. T. (Lab. Environmental Chemistry, Univ. Amsterdam, Nieuwe Achtergracht 166, Amsterdam, The Netherlands); Bruggeman, W. A.; Hutzing-er, O. *Experientia* 33(9): 1134-1136; 1977.

Dechlorinated products were detected in the urine of male Wistar rats fed 4,4'-dichloro-3-biphenylol, 4,4'-dichloro-3,3'-biphenyldiol, 3-chloro-4-biphenylol and 2,6-dichlorophenol. A direct metabolic dechlorination is thus indicated, as opposed to dechlorination via arene oxides with concomitant hydroxylation. (13 refs.)

77-5485 Enhancement of 2-Hydroxylation In Vitro of Biphenyl by Organochlorine Insecticides. (Eng)

Tong, S. (Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England); Ioannides, C.; Parke, D. V. *Biochem Soc Trans* 5(5): 1374-1377; 1977.

The carcinogenic potential of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) and its major metabolites, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane (DDD), was evaluated by the biphenyl test in vitro. DDT and DDD enhanced the 2-hydroxylation of biphenyl with microsomal fractions from male Wistar rats, male CF-1 mice (6 wk old), and adult polecat ferrets. DDE had either no effect or caused a decrease in enzyme activity. The enhancement of biphenyl 2-hydroxylase by DDT and DDD was concentration-dependent, with max stimulation occurring at 3 mM. Activation of the biphenyl 2-hydroxylase system by DDT and DDD may involve dechlorination, with formation of a complex with cytochrome P-450. (14 refs.)

77-5486 Toxicity of Polybrominated Biphenyl (Letter to Editor). (Eng.) Kimbrough, R. D. (Center for Disease Control, Atlanta, GA 30333); Burse, V. W.; Liddle, J. A.; Fries, G. F. *Lancet* 2(8038): 602-603; 1977.

Studies with rats exposed to polybrominated biphenyl indicated that the compound is eliminated slowly, persisting in the liver where the resulting lesion progresses into neoplasia. It is not known whether the retention is due to enterohepatic recirculation or to the inability of the rat to excrete the compound, nor whether these results can be extrapolated to humans. (8 refs.)

77-5487 Repair of Rat Liver DNA In Vivo Damaged by Ethylene Dibromide. (Eng) Nachtomi, E. (Fels.

Res. Inst., Dept. Pathology, Temple Univ. Sch. Medicine, Philadelphia, PA 19104); Sarma, D. S. *Biochem Pharmacol* 26(20): 1941-1945; 1977.

Tube feeding of [¹⁴C]ethylene dibromide (EDB) to non-fasted Wistar rats resulted in the incorporation of the radioactivity into liver DNA, RNA, and protein. The pesticide caused slower sedimentation of liver DNA in alkaline but not in

neutral sucrose gradients. The slower sedimentation of liver DNA in alkaline sucrose gradients was apparent within 2 hr after the administration of a dose of 22 mg/100g body wt or 4 hr after a dose of 7.5mg/100g. The liver DNA damage induced by EDB at 7.5 mg/100 g was repaired significantly by 17.5 hr and almost completely by 96 hr. Administration of diethyldithiocarbamate, a free radical scavenger, did not inhibit liver DNA damage caused by EDB. The results indicate that EDB produces both chemical and physical lesions in liver DNA. (39 refs.)

77-5488 Carcinogenicity of Trichloroethylene: Fact or Artifact? (Eng.) Henschler, D. (Institut für Toxikologie, Universität Würzburg, Versbacher Landstrasse 9, D-8700 Würzburg, W. Germany); Eder, E.; Neudecker, T.; Metzler, M. *Arch Toxicol* 37(3): 233-236; 1977.

Because trichloroethylene (TCE) was previously reported to produce a high incidence of hepatocellular carcinomas in mice (but not rats) after high daily doses po, this compound was studied further. Analysis of a sample of technical grade TCE (same as that used in the bioassay experiment for carcinogenicity) by gas chromatography/mass spectrometry showed the presence of two major contaminants, epichlorohydrin and 1,2-epoxybutane, both of which were found to be highly mutagenic in the Ames test using *Salmonella typhimurium* TA100. A low activity was found for trichloroethylene itself, and no activity was found for the other contaminants (diisobutylene, carbon tetrachloride, chloroform, and 1,1,1-trichloroethane). The carcinogenic effect of TCE is concluded to be due to epichlorohydrin and epoxybutane. (10 refs.)

77-5489 Mutagenicity of Ethylene Oxide and Associated Health Hazard (Meeting Abstract). (Eng.) Embree, J. W. (Univ. California, San Francisco, CA 94143). *Diss Abstr Int B* 38(3): 1158; 1977. (no refs.)

77-5490 Histopathology of Carcinomas of the Liver in Mice Ingesting Heptachlor or Heptachlor Epoxide. (Eng) Reuber, M. D. (11014 Swansfield Road, Columbia, MD 21004). *Exp Cell Biol* 45(3/4): 147-157; 1977.

Male and female C3HeB/Fe mice received 10 ppm heptachlor or 10 ppm heptachlor epoxide in their diet for up to 24 mo. Liver carcinomas developed in 64/87 males and 57/78 females ingesting heptachlor and in 73/79 males and 77/81 females ingesting heptachlor epoxide. The carcinomas varied from well-differentiated to poorly differentiated and undifferentiated, and they were capable of invasion and metastasis. (13 refs.)

77-5491 **Models for the Enzymatically Active State of Cytochrome P-450.** (Eng.) Loew, G. H. (Dept. Genetics, Stanford Univ. Medical Center, Stanford, CA 94305); Hjelmeland, L. M.; Kirchner, R. F. *Int J Quantum Chem Quantum Biol Symp* (4): 225-244; 1977.

Ab initio and semiempirical molecular orbital calculations were made for a heme-containing model of the biologically active state of cytochrome P-450 and for two chemical models of the enzyme, chromyl chloride (CrO_2Cl_2) and peroxytrifluoroacetic acid (CF_3COOOH), known to yield similar oxidation products. The heme model for the transient activated state of P-450 was derived by analogy to a more stable active complex (compound I) formed by another heme enzyme, horseradish peroxidase, with peroxides. The main aim of these studies was to characterize the active state and, in particular, the electrophilic oxygen transferred to substrates by these enzymes. All models for the active state of P-450 have negatively charged oxygen atoms and low-energy virtual or half-filled orbitals with a substantial oxygen character. These combined results suggest that the electrophilic activity of the oxygen in all these compounds is related to overlap, rather than to charge-controlled interactions with nucleophilic substrates. Calculations for a model of compound I itself yield a π cation porphyrin radical with two unpaired electrons in highly covalent, nearly degenerate iron-oxygen orbitals. Electric field gradients and quadrupole splittings calculated for both compound I and its reduced form (compound II) are in good agreement with the experimental data. (72 refs.)

77-5492 **The Effect of Dietary Conjugated Protein Levels and Vitamin A on the Induction of Cytochrome P-450 by DDT in the Rat.** (Fre.) Ferrando, R. (Laboratoire de Nutrition et d'Alimentation, Ecole nationale vétérinaire, 94701 Alfort, France); Truhaut, R.; Gak, J. C.; Braillet, C.; Furlon, C. *CR Acad Sci [D] (Paris)* 284(23): 2419-2421; 1977.

Ingestion of 5% protein and vitamin A (25 μg) by rats caused no significant change in the induction of cytochrome P-450 in the liver due to DDT (5 mg), but simultaneous intake of 5% protein and vitamin A increased the induction of cytochrome P-450 significantly. In the absence of vitamin A, however, the induction of cytochrome P-450 was similar with 0% or 15% protein. (3 refs.)

77-5493 **Test for Carcinogenicity of Organic Contaminants of United States Drinking Waters by Pulmonary Tumor Response in Strain A Mice.** (Eng.) Theiss, C. (Dept. Community Medicine, M-014, Sch. Medicine, Univ. California at San Diego, La Jolla, CA 92093); Stoner, J. D.; Shimkin, M. B.; Weisburger, E. K. *Cancer Res* 37(8, part 1): 2717-2720; 1977.

The production of lung adenomas in strain A mice was investigated after multiple ip injections of the following organic contaminants of drinking water: chloroform, 1,2-dichloroethane, 1,1,2,2-tetrachloroethylene, hexachloro-1,3-butadiene, 2-chloroethyl ether, triphenyl phosphate, butyl benzyl phthalate, octyl chloride, bromoform, bromodichloromethane, dichloromethane, 1,1,2,2-tetrachloroethane, 1,1,3,3-tetrachloroacetone, 4-bromodiphenyl ether, hexachlorocyclohexane, hexachlorobenzene, and urethan. Of these, only bromoform produced a pulmonary adenoma response that was significantly greater than that of vehicle-treated control mice. A total dose of 1,100 mg of bromoform given in 23 applications increased the incidence of lung tumors per mouse from 0.19 to 1.13. (19 refs.)

77-5494 **Mutagenicity and Rat Liver Induction by Tap Water Contaminants as Determined by Bacterial Mutagenesis (Meeting Abstract).** (Eng.) Schoeny, R. (Dept. Microbiology, Univ. Cincinnati, Cincinnati, OH 45221); Loper, J. C. *Clin Res* 25(4): 634A; 1977. (1 ref.)

77-5495 **Evidence for Existence in Human Tissues of Monomers for Plastics and Rubber Manufacture.** (Eng.) Wolff, M. S. (Environmental Sciences Lab., Dept. Community Medicine, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY 10029) *Environ Health Perspect* 17: 183-187; 1976.

Discussion concerns the storage in fat of lipophilic substances such as DDT, polychlorinated biphenyls, tetrachloroethylene, and trichloroethylene, which are chemically similar to many industrially-used monomers, plus styrene, acrylamide, and vinyl chloride. Data on the uptake, metabolism, storage, and excretion of these substances in humans are provided when available. The storage and removal of lipophilic substances from fat tissues depend on fat solubility, volatility, and metabolism. Styrene is very soluble in blood and fat: following exposure at 100 ppm, blood levels of 0.2-15 ppm styrene have been determined. The urinary and breath half-lives of styrene metabolites and styrene, respectively, are about 8 hr and 1-3 hr, respectively. Detectable levels of styrene were present in the fat of styrene workers > 2 days following exposure, a much longer period than that over which styrene could be detected in the breath of people experimentally exposed to 100 ppm styrene for sustained periods. (28 refs.)

77-5496 **Chromosomal Damage in Men Occupationally Exposed to Vinyl Chloride Monomer and Other Chemicals.** (Eng.) Heath, C. W. (Cancer and Birth Defects Div., Bureau Epidemiology, Center Disease Control, Public

Health Service, U.S. Dept. Health, Education and Welfare, 1600 Clifton Road, N. E., Atlanta, GA 30333; Dumont, C. R.; Gamble, J.; Waxweiler, R. J. *Environ Res* 14(1): 68-72; 1977.

Cytogenetic analyses were conducted on men employed at a rubber and plastics plant who were exposed to vinyl chloride monomer (VCM). Frequencies of chromosomal damage were measured in the peripheral blood lymphocytes of 35 men employed for ≥ 10 yr: 14 in polyvinyl chloride (PVC) polymerization (high-exposure group), 4 in PVC processing (low exposure group), and 17 in rubber tire manufacture (negligible exposure group). In addition, four nonindustrial employees who had not been exposed to laboratory chemicals were included (controls). Breakage levels were significantly higher in all three test groups than in the controls. Chromatid gaps comprised the majority (86%) of aberrations seen. However, overall breakage levels were similar in the three industry groups, which indicates that VCM was not the sole cause of the damage. (9 refs.)

77-5497 An Ovary-dependent Mouse Mammary Tumor Induced by Urethan. (Eng.) Matsuzawa, A. (Lab. Animal Res. Center, Inst. Medical Science, Univ. Tokyo, Shirogane-dai 4-6-1, Minato-ku, Tokyo 108, Japan); Yamamoto, T.; Mizuno, Y. *Gann* 68(4): 523-524; 1977.

A hormone-dependent transplantable mammary tumor was induced by urethan in female BALB/c mice having no mouse mammary tumor virus in their milk. Histologically, the tumor was an adenocarcinoma and was designated UHDMT-26. Further studies are in progress. (5 refs.)

77-5498 Influence of the Tissue-specific Pulmonary Adhesive Factor on Induction of Lung Adenomas by Urethane in Mice. (Rus.) Modianova, E. A. (Dept. Carcinogenesis, Oncological Scientific Center, Acad. Medical Sciences USSR, Moscow, USSR); Malenkov, A. G.; Shabad, L. M. *Biull Eksp Biol Med* 34(8): 193-196; 1977.

The effect of tissue-specific pulmonary adhesive factor (AF, ip administered) on pulmonary adenoma induction by urethane (0.5 or 0.25 mg/g sc) was measured by a nuclei isolation assay in line A mice. Urethane alone induced multiple pulmonary adenomas in all mice. AF, administered in doses that reduce the isolation of nuclei during standard dispersion (10^{-7} - 10^{-6} mg/g for the nonsterilized preparation, 10^{-4} - 10^{-5} mg/g for the sterilized preparation) decreased the tumor-inducing effect of urethane. A significant reduction (to 75%-81%, $p < 0.05$ - 0.001) was observed with AF doses at the lower end of the lower dose range. When AF was administered in doses which increase the isolation of nuclei (10^{-4} - 10^{-5} mg/g for the nonsterilized preparation) it either had no effect on tumor induction or it increased the number of tumors per animal. (8 refs.)

77-5499 Increased Guanylate Cyclase Activity and Guanosine 3', 5'-Monophosphate Content in Ethionine-induced Hepatomas. (Eng.) DeRubertis, F. R. (Dept. Medicine, Veterans Admin. Hosp., Pittsburgh, PA 15240); Craven, P. *Cancer Res* 37(1): 15-21; 1977.

The properties of the guanylate cyclase (GC)-cyclic guanosine 3', 5'-monophosphate (cGMP) system of ethionine-induced Wistar rat hepatomas were examined. The cGMP levels of the hepatomas, determined in specimens quick-frozen in situ and after in vitro incubation of tissue slices, were approx two times higher than those of surrounding tissue or control livers. Higher cGMP activity in the tumors was associated with an increase in whole homogenate, soluble, and particulate GC activities as well as with an increase in soluble cGMP-phosphodiesterase activity. 3-Isobutyl-1-methylxanthine, a potent inhibitor of cGMP-phosphodiesterase activity, potentiated the differences in cGMP between the hepatomas and surrounding liver or control liver, suggesting that the higher steady-state cGMP content of the tumors reflected enhanced basal cGMP synthesis that was partially offset by increased nucleotide degradation. In the hepatomas, a greater proportion of the total GC activity was located in the particulate cell fraction (31%), compared with the subcellular distribution of enzyme activity in either surrounding liver or controls (15% of total in the particulate fraction). Carbamylcholine increased cGMP threefold in surrounding liver and controls, but it did not alter hepatoma cGMP levels. Further, the relative increase in cGMP and GC activities of the tumors in response to NaN_3 , NH_2OH , and NaNO_2 were blunted compared to surrounding liver or controls. Ethionine-induced hepatomas are, therefore, characterized by (1) significant increases in cGMP content and in GC and cGMP-phosphodiesterase activities, (2) a change in the subcellular distribution of GC, and (3) altered responsiveness of the GC-cGMP system to several agonists. (52 refs.)

77-5500 1,2-Dimethylhydrazine-induced Tumors in CBA Mice. (Rus.) Turusov, V. S. (Lab. Carcinogenic Substances, Oncological Res. Center, Acad. Medical Sciences USSR, Moscow, USSR); Lanko, N. S.; Bazlova, L. S. *Vopr Onkol* 23(7): 39-43; 1977.

The carcinogenic effect of 1,2-dimethylhydrazine (DMH; 8 mg/kg sc, 1x/wk), administered with or without trichlorfon (0.04% in drinking water) for 38-40 wk, was studied in 2- to 3-mo-old CBA mice. In the group treated with DMH and trichlorfon, the first tumors appeared after 22-25 wk; in the group treated with DMH, they appeared after 27-33 wk. Otherwise, trichlorfon had no influence on the incidence and localization of the tumors induced, and it was not carcinogenic when administered alone. All but 1/43 mice developed tumors, most of which were multiple. Uterine tumors (endometrial sarcomas, tumors with myometrial and vascular components) were found in 28 mice, intestinal tumors in 26,

mal tumors (squamous cell or squamous-basal cell carcinomas, small sebaceous adenomas, small basal cell tumors) 26, hemangio-endotheliomas of the liver in 15, ovarian angiomas in 4, fibrous polyposis of the forestomach in 3, pulmonary hemangioendothelioma in 1, reticulum cell sarcoma of the large intestine in 1, and renal adenoma in 1. The findings indicate that DMH appears to be a more polytropic carcinogen in CBA mice than in rats. (13 refs.)

77-5501 Changes in Cell Population Kinetics of Enterocytes During Colonic Tumor Development in Rats. (Rus.) Pozharisskii, K. M. (Lab. Experimental Tumors, Scientific Res. Inst. Oncology, Leningrad, USSR.); Limashevskii, V. F.; Gushchin, V. A. *Tsitologiya* 19(7): 768-80; 1977.

The population kinetics of enterocytes in the descending colon were studied in random-bred male rats during the induction of colon tumors by 1,2-dimethylhydrazine dihydrochloride (21 mg/kg/wk, sc). Carcinogen-induced disturbances in enterocyte differentiation led to a broadening of the proliferative crypt zone, with proliferating cells appearing even in the isthmia of the crypts. These superficial parts of the crypts later proved to be the sites of carcinomas in situ. Starting from the first month, the mitotic cycle of the enterocytes increased from 11 hr to 15-16 hr because of the prolongation of G₁. Three subpopulations with different mitotic cycles (11, 21, and 28 hr) appeared in the zones of max proliferation. The mitotic cycle of 90%-95% of the enterocytes was short (about 11 hr) in microscopically normal intestinal mucosa, as well as in carcinoma in situ and superficial cancer. Starting from the first month, the number of pathological mitoses (bridges, failure of chromosomes to migrate properly, three-group metaphases, monocentric and pluripolar mitoses) amounted to 50-51%, and remained at this high level 2-3 mo after termination of treatment; ie, the abnormal mitoses were not due to the toxic effect of the carcinogen. (27 refs.)

77-5502 Dimethylhydrazine-induced Colon Tumors in Rats Fed Diets Containing Beef Fat or Corn Oil With and Without Wheat Bran. (Eng) Wilson, R. B. (Dept. Veterinary Microbiology and Pathology, Washington State Univ., Pullman, WA 99163); Hutcheson, D. P.; Wideman, R. *Am J Clin Nutr* 30(2): 176-181; 1977.

The time of onset, incidence, and type of tumors induced by dimethylhydrazine (DMN: 30 mg/kg/wk x 4 or 8, by gastric intubation) in male Sprague-Dawley rats fed diets containing corn oil or beef fat, with or without wheat bran as a source of fiber, were investigated. The colon tumor incidence in rats given four doses of DMN, beef fat, and no bran was 68% (1.9 tumors/rat), but a tumor incidence of only 38% (1.1 tumors/rat) occurred in rats receiving the same treatment with bran; the difference was statistically significant. The figures for four

DMN doses with corn oil and no bran and corn oil and bran were 65% (1.5 tumors/rat) and 43% (1.6 tumors/rat); this difference was not significant. In rats given eight doses, beef fat, and no bran the tumor incidence was 70% (3.0 tumors/rat); with bran, the figure was 63% (3.1 tumors/rat). A significant difference was noted between rats given eight doses, corn oil, and no bran (90% incidence, 2.8 tumors/rat) and those given bran (66% incidence, 3.7 tumors/rat). The overall significant figures were 52% and 75% tumor incidences in rats fed bran and no bran, respectively, and 53% (1.3 tumors/rat) and 74% (3.1 tumors/rat) incidences in animals that received four and eight DMN doses, respectively. The earliest deaths occurred in rats receiving corn oil (5 mo), which was also significant. The percentage of rats with polypoid colonic neoplasms was higher in rats fed no bran, but there was no significant difference in the percentage of rats with malignant colonic tumors with respect to feeding of bran. (15 refs.)

77-5503 Formation of O⁶-Methylguanine by Alkylation of Rat Liver, Colon, and Kidney DNA following Administration of 1,2-Dimethylhydrazine. (Eng) Rogers, K. J. (Dept. Physiology, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA 17033); Pegg, A. E. *Cancer Res* 37(11): 4082-4087; 1977.

The alkylation of DNA in the Sprague-Dawley rat liver, kidney, and colon was measured at varying times after administration of 1,2-dimethylhydrazine (DMH). DNA was alkylated to a much greater extent in the liver than in the kidney or colon after a dose of 200 mg/kg ip or sc. Alkylation of kidney DNA was greater after sc injection than after ip injection, but the reverse was true in the colon. Several methylated purines were detected in DNA hydrolysates from rats given ¹⁴C-DMH. These included 7-methylguanine, O⁶-methylguanine (MeG), 3-methyladenine, 1-methyladenine, and 7-methyladenine. The relative amounts of these products were consistent with the hypothesis that alkylation was mediated via the metabolism of DMH to an alkylating species similar to that generated by dimethylnitrosamine and N-methyl-N-nitrosourea. Substantial amounts of MeG formed in the colon DNA after injection of DMH, and it was not lost rapidly from the DNA. However, MeG was present in greater amounts in the liver than in the colon or kidney at all times after 200 mg/kg DMH. Since the liver is not a target organ for DMH carcinogenesis, factors other than MeG production must be important in tumor initiation. The findings are discussed in relation to the hypothesis that the formation and persistence of MeG throughout DNA replication may initiate neoplasia by carcinogens that yield methylating agents. (37 refs.)

77-5504 Detection of Activated Anions in Rat Liver Mitochondria Using Rutamycin and Hydrazine

(or 1,2-Dimethylhydrazine) as Probes (Meeting Abstract). (Eng.) Cook, G. L. (Southern Illinois Univ., Carbondale, IL 62901). *Diss Abstr Int [B]* 38(2): 640; 1977. (no refs.)

77-5505 Covalent Interaction of Dehydroretronecine, a Carcinogenic Metabolite of the Pyrrolizidine Alkaloid Monocrotaline, with Cysteine and Glutathione. (Eng.) Robertson, K. A. (Dept. Pathology, Univ. Wisconsin Medical Sch. Madison, WI 53706); Seymour, J. L.; Hsia, M. T.; Allen, J. R. *Cancer Res* 37(9): 3141-3144; 1977.

The alkylating ability of dehydroretronecine (DHR) was examined by identifying the structure of the reaction products of DHR with cysteine and glutathione in vitro. DHR was prepared from the parent pyrrolizidine alkaloid monocrotaline. Sulfhydryl-linked 7-thiocysteine-DHR and 7-thioglutathione-DHR were the major reaction products according to spectral, chromatographic, and qualitative data. The nucleophilic sulfhydryl group serves as one potential target for alkylation by the pyrrole. (19 refs.)

77-5506 Inhibitory Effect of a Polychlorinated Biphenyl (Aroclor 1254) on Aflatoxin B₁ Carcinogenesis in Rainbow Trout (*Salmo gairdneri*). (Eng.) Hendricks, J. D. (Dept. Food Science and Technology, Oregon State Univ., Corvallis, OR 97331); Putnam, T. P.; Bills, D. D.; Sinnhuber, R. O. *J Natl Cancer Inst* 59(5): 1545-1551; 1977.

The effect of Aroclor 1254 (a polychlorinated biphenyl) on the hepatocarcinogenicity of aflatoxin B₁ (AFB₁) in rainbow trout (*Salmo gairdneri*) was investigated. Fingerlings were fed a diet containing 6 ppb AFB₁, 100 ppm Aroclor 1254, or 6 ppb AFB₁ + 100 ppm Aroclor 1254. The experiment was terminated at 1 yr. The growth rate was significantly reduced by AFB₁ and AFB₁ + Aroclor, but fish receiving the combination had a significantly higher growth rate than those receiving AFB₁ only. The concentration of Aroclor on a whole-fish basis increased for the first 6 mo and then plateaued at approx 80 ppm. However, absolute quantities continued to increase, in parallel with growth curves. The amount of Aroclor in the lipid fraction decreased from 6 to 12 mo. No tumors were noted prior to 9 mo, but 26/37 AFB₁ fish and 14/46 AFB₁ + Aroclor fish had tumors at 12 mo. Tumors were smaller in the latter fish. Control fish and those fed Aroclor only did not have any liver tumors. These findings are highly significant. The livers of fish fed Aroclor or Aroclor + AFB₁ had less glycogen and displayed AFB₁ damage; their spleens had reduced amounts of white pulp and varying degrees of hyperemia. The kidneys of all animals exhibited degenerative changes. It is concluded that 100 ppm Aroclor has a minimal effect on the well-being of rainbow trout, but it significantly reduces the risk of AFB₁-induced carcinogenesis. (39 refs.)

77-5507 Formation of Aflatoxin B₁ from Aflatoxicol by Rainbow Trout (*Salmo gairdneri*) Liver In Vitro. (Eng.) Loveland, P. M. (Dept. Food Science and Technology, Oregon State Univ., Corvallis, OR 97331); Sinnhuber, R. O.; Berggren, K. E.; Libbey, L. M.; Nixon, J. E.; Pawlowski, N. E. *Res Commun Chem Pathol Pharmacol* 16(1): 167-170; 1977.

The submitochondrial fraction of homogenized livers from 2-yr-old Mt. Shasta rainbow trout was incubated with aflatoxin B₁ (AFB₁; a milliM total) and an NADPH generating system for 1 hr at 25 C, and at a pH of 7.2. High pressure liquid chromatography of the extract obtained following incubation showed a 5% to 27% yield of aflatoxicol (R₀), the major AFB₁ metabolite produced in vitro. When synthetic aflatoxicol isomers were similarly incubated with the submitochondrial fraction, AFB₁ was found to be the main product. The ability of trout postmitochondrial enzymes to convert R₀ back to AFB₁ may be significant in explaining the extreme sensitivity of trout to AFB₁. The apparent carcinogenicity of R₀ may be due to its conversion to AFB₁ in susceptible animals or to the formation of its own carcinogen by the action of microsomal enzyme (10 refs.)

77-5508 Comparative In Vitro Metabolism of Aflatoxicol by Liver Preparations from Animals and Humans. (Eng.) Salhab, A. S. (Dept. Pharmacology, Georgetown Univ. Medical Center, Washington, DC 20037); Edwards, G. S. *Cancer Res* 37(4): 1016-1021; 1977.

The metabolism of ¹⁴C-aflatoxicol (AFL) by liver postmitochondrial and microsomal fractions from humans and eight other species was compared. A major metabolic pathway involved the dehydrogenation of AFL to yield aflatoxin E (AFB₁). Human liver preparations were more active in this respect than preparations from the four other species tested (monkey, rat, mouse, and dog). The AFL dehydrogenase activity was associated mainly with the microsomal fraction and required a hydrogen receptor (eg, NADP). The enzyme was not inhibited by carbon monoxide, indicating that it was independent of the heme-containing microsomal drug-metabolizing system. Postmitochondrial liver fractions also oxidized AFL to at least five other metabolites that comigrated on thin-layer chromatography was aflatoxins Q₁, P₁, H₁, and B₂a. None of these metabolites were formed in the presence of carbon monoxide. Liver cytosol fractions from the rabbit and trout, two species that are very sensitive to AFB₁, were the most active in converting AFB₁ to AFL. This activity was almost absent in the guinea pig. Preparations from monkey, human, hamster, rat, and mouse liver showed intermediate activity. (21 refs.)

77-5509 Nuclear Magnetic Resonance Identification of Versiconal Hemiacetal Acetate as an Intermediate

ate in Aflatoxin Biosynthesis. (Eng) Fitzell, D. L. (Dept. Environmental Toxicology, Univ. California, Davis, CA 95616); Singh, R.; Hsieh, D. P.; Motell, E. L. *J Agric Food Chem* 25(5): 1193-1197; 1977.

A pigment previously identified as versiconal acetate that is an intermediate in aflatoxin synthesis was prepared from radioactively labeled sodium acetate using dichlorvos-related cultures of *Aspergillus parasiticus*. Attempts were made to assign a structure to this intermediate structure by ^{13}C and ^1H pulsed Fourier transform nuclear magnetic resonance analyses. The data indicate that this pigment is versiconal hemiacetal acetate. (20 refs.)

77-5510 Mutagenicity of Fungal Metabolites Related to Aflatoxin Biosynthesis. (Eng) Wong, J. J. (Dept. Environmental Toxicology, Univ. California, Davis, CA 95616); Singh, R.; Hsieh, D. P. *Mutat Res* 44(3): 447-450; 1977.

The mutagenicity of aflatoxin B_1 (AFB_1) and several of its biosynthetic intermediates was assayed using *Salmonella typhimurium* strain TA98. The relative mutagenic potencies of these compounds, which coincided with their sequential order in the biosynthetic pathway, were: norsolorinic acid, 0.18% at 0-8.0 $\mu\text{g}/\text{plate}$; averufin, 0.19% at 0-4.0 μg ; versiconal acetate, 0.21% at 0-4.0 μg ; versicolorin A, 5.83% at 0-0.8 μg ; sterigmatocystin, 10.66% at 0-0.1 μg ; and AFB_1 , 100% at 0-0.1 $\mu\text{g}/\text{plate}$. Versicolorin A and sterigmatocystin were considered significant mutagens relative to AFB_1 . The absence of the unsaturated bisfuran structure in norsolorinic acid, averufin, and versiconal acetate, the three compounds that did not exhibit significant mutagenicity, further supports the requirement of this structure for the mutagenicity and carcinogenicity of aflatoxins and related compounds. However, although the bisfuran moiety appears essential for mutagenicity, and not the anthraquinone moiety, it is not the sole determinant. The configuration and electronic structure of the entire molecule are also key factors. (16 refs.)

77-5511 Comparison of the Genetic Activity of Aflatoxins B_1 and G_1 in *Escherichia coli* and *Saccharomyces cerevisiae*. (Eng) Callen, D. F. (Environmental Mutagenesis Branch, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC 22709); Mohn, G. R.; Ong, T. M. *Mutat Res* 45(1): 7-11; 1977.

The ability of aflatoxin B_1 and aflatoxin G_1 to induce back mutations to *arg+* in *Escherichia coli* K-12/343/113 was compared with the induction of mitotic gene conversion to *de+* in the diploid yeast strain *Saccharomyces cerevisiae* D4, *de* $_2$ -. Similar to previous results with other microorganisms, the compounds were not genetically active per se, which indi-

cates that the tester strains were unable to activate the compounds to mutagenic products. In experiments using liver homogenates (S-9 fraction) of male Syrian Golden hamsters pretreated with phenobarbital, aflatoxin B_1 exhibited strong genetic activity both in *E. coli* and in *S. cerevisiae*. The mutagenicity of aflatoxin G_1 was markedly lower and could be detected only in the *E. coli* tester strain. These results corroborate the findings that aflatoxin G_1 is a less potent carcinogen and mutagen than aflatoxin B_1 . (17 refs.)

77-5512 Milk Aflatoxin and Toxicity Transfer. (Fre.) Ferrando, R. (Laboratoire de Nutrition et d'Alimentation, Ecole nationale Veterinaire, 94701 Alfort); Parodi, A.; Henry, N.; Delort-Laval, J.; N'Diaye, A. L. *C R Acad Sci [D] (Paris)* 284(10): 855-858; 1977.

Lactating goats were fed three types of peanuts containing 1,530, 79, and 54 $\mu\text{g}/\text{kg}$ total aflatoxins and 1,136, 64, and 54 $\mu\text{g}/\text{kg}$ aflatoxin B_1 , respectively, and their milk was lyophilized. In the group consuming peanuts with the highest concentration of total aflatoxin, the dried milk products contained 0.5 $\mu\text{g}/\text{kg}$ aflatoxin B_1 , traces of aflatoxin B_2 , and 16.2 $\mu\text{g}/\text{kg}$ of aflatoxin M_1 . Milk from all other experimental groups showed no presence of mycotoxin. These dried milk products were given as 20% of their total food ration, to ducklings on days 1 to 23. No adverse effect on growth, feeding, or liver or kidney histology was noted. In contrast, direct consumption by the ducklings of peanut meal with the highest levels of aflatoxin produced an 18% mortality rate and characteristic lesions of aflatoxicosis. (3 refs.)

77-5513 Analysis of Aflatoxins in Stored Grain. (Rum.) Galea, V. (Laboratorul de Toxicologie, Institutul Oncologie Cluj-Napoca, Cluj-Napoca, Romania); Bara, A. *Igiena (Bucharest)* 25(3): 207-209; 1976.

Forty-two stored grain samples were analyzed for aflatoxins. Aflatoxin B_1 was detected in two samples with a moldy odor. Aflatoxin M_1 was also tentatively identified in one of these samples. (8 refs.)

77-5514 Determination of Patulin in Apple Juice Products as the 2,4-Dinitrophenylhydrazine Derivative. (Eng.) Stinson, E. E. (Eastern Regional Res. Center, Agricultural Res. Service, U.S. Dept. Agriculture, Philadelphia, PA 19118); Huhtanen, C. N.; Zell, T. E.; Schwartz, D. P.; Osman, S. F. *J Agric Food Chem* 25(5): 1220-1222; 1977.

A useful method for determining patulin (4-hydroxy-4H-

furo[3,2-c]pyran-2(6*H*)-one) as the 2,4-dinitrophenylhydrazone derivative in apple juice products was developed. The lower limit for detection was approx 50 ppb in a 50 μ l sample of apple juice or cider. (12 refs.)

- 77-5515 **The Fate of Ochratoxin A in Rats.** (Eng.) Chang, F. C. (Food Res. Inst., Univ. Wisconsin, Madison, WI 53706); Chu, F. S. *Food Cosmet Toxicol* 15(3): 199-204; 1977.

Toxicologic studies were conducted on rats receiving single ip injections of 1 mg of 14 C-labeled ochratoxin (OA). OA reached its highest levels in the serum (equivalent to approx 90% of the dose), liver (4.5%), and kidney (4.4%) 30 min after injection and then decreased gradually, although at 24 hr the samples still contained up to 1 μ g OA/g. Electrophoresis of rat serum demonstrated that OA was predominantly bound to the serum albumin fraction in vivo. The toxin was excreted primarily via the urine (over 50% during the first 24 hr) either in its original form (approx 45%) or as unidentified metabolites. Only 13% of the injected OA was excreted in the feces within the first 24 hr, and 77% of this was unaltered OA. On the basis of these data, it is recommended that the meat and organs of animals suffering from mycotoxic nephropathy be rejected for food use because of possible contamination with OA or other mycotoxins. (23 refs.)

- 77-5516 **Regeneration of Rat Liver in the Presence of Essential Oils and Their Components.** (Eng.) Gershbein, L. L. (Northwest Inst. Medical Res., 5656 W. Addison St., Chicago, IL 60634). *Food Cosmet Toxicol* 15(3): 173-181; 1977.

Liver regeneration was studied over a 10-day period in partially hepatectomized rats (1) given daily sc injections of high levels of essential oils, terpenes, or aromatic compounds for the first 7 days or (2) fed ad libitum for 10 days on diets supplemented with these agents. Liver regeneration was increased significantly by sc injection of the oils of anise, fennel, tarragon, parsley seed, celery seed and oleoresin, nutmeg, mace, cumin, and sassafras and of the aromatic principles 4-allylanisole, 4-propenylanisole, p-isopropylbenzaldehyde, safrole, and isosafrole. Most of the essential oils were ineffective in doses up to 3,000 mg/kg because they contained large quantities of terpenes, which were found to be inert. Many of the agents effective by the sc route were also active when added to the diet. Several agents increased the wet and dry liver wt in intact rats when given by either route. Because of the short period of investigation, morphologic findings in the liver were not remarkable, even though the administered doses were massive. (42 refs.)

- 77-5517 **Excretion and Metabolism of Tritiated Diethylstilbestrol in the Female C3H Mouse (Meeting Abstract).** (Eng.) Helton, E. D. (Hormone Res. Program, Natl. Center for Toxicological Res., Jefferson, AR); Gough, B. J. *J Toxicol Environ Health* 3(1/2): 352-353; 1977. (no refs.)

- 77-5518 **Altered Surface Epithelium in the Female Mouse Genital Tract Following Prenatal Exposure to Diethylstilbestrol (Meeting Abstract).** (Eng.) McLachlan, J. A. (Environmental Toxicology Branch, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC); Lamb, J. C.; Stumpf, W. W.; Newbold, R. R. *J Toxicol Environ Health* 3(1/2): 366; 1977. (no refs.)

- 77-5519 **Binding of DES and E2 to Plasma Proteins (Meeting Abstract).** (Eng.) Sheehan, D. M. (Hormone Res. Program, Natl. Center for Toxicological Res., Jefferson, AR). *J Toxicol Environ Health* 3(1/2): 371; 1977. (no refs.)

- 77-5520 **Cytologic Evaluation of the Effect of Various Estrogens Given in Postmenopause.** (Eng.) Hustin, J. (Institut de Morphologie Pathologique, B-6270, Loverval, Belgium) Van den Eynde, J. P. *Acta Cytol* 21(2): 225-228; 1977.

A cytological study was undertaken of 236 postmenopausal or hysterectomized women during hormone treatment and at various times after estrogen withdrawal. The initial menopausal status and its evolution under treatment were assessed by the maturation value (MV). The maturation index was evaluated after a differential count of 400 cells. The MV was determined by multiplying the percentage of each cell type by an arbitrarily assigned value for that cell type: 0.2 for parabasal cells, 0.6 for intermediate cells and 1.0 for superficial cells. During the first week of po administration of estradiol derivatives or dienestrol, there was a steep rise of the MV (> 60) after 48 hr; with estriol, the rise was very slow regardless of dosage (MV = 27). At the end of the second week of treatment, the MV was always > 60, except in the case of estriol at doses < 2 mg/wk (MV = 25). Pure estradiol derivatives or estrogen compound and testosterone quickly initiated a sharp increase of the MV when given parenterally. Two months after injection, the MV was still \geq 60. Sc pellets of diethylstilbestrol also induced a very high MV that remained at that level for at least 18 mo after implantation. Although estriol has a considerably weaker action than

tradiol derivatives, it is recommended for the po treatment of local changes due to atrophy, since it is effective at the vaginal level in doses three to five times lower than those necessary to induce endometrial proliferation. (11 refs.)

77-5521 **FDA Studies of Estrogen, Progestogens, and Estrogen/Progestogen Combinations in the Dog and Monkey.** (Eng.) Geil, R. G. (International Res. and Development Corporation, Mattawan, MI); Lamar, J. K. *J Toxicol Environ Health* 3(1/2): 179-193; 1977.

Studies on the effects of various estrogen, progestogen and estrogen/progestogen preparations in female beagle dogs and male rhesus monkeys are reported. Neither benign nor malignant liver tumors were observed in either species. Mammary changes induced in dogs with some of the preparations are described. Other complications in both species are reported. (2 refs.)

77-5522 **Studies of a Progestogen (MGA) as Related to Residues and Human Consumption.** (Eng.) Lauderdale, J. W. (Agricultural Res., Upjohn Co., Kalamazoo, MI 49001); Goyings, L. S.; Krzeminski, L. F.; Zimbelman, G. *J Toxicol Environ Health* 3(1/2): 5-33; 1977.

The hormonal activity of melengestrol acetate (MGA), an orally active progestogen marketed for improved feed utilization, growth stimulation, and estrus suppression of feedlot steers, was investigated in humans, rhesus monkeys, cattle, dogs, rabbits, mice, and rats. The biologic activities were dose-dependent within each species and predictable; ie, block ovulation and the menstrual or estrous cycle. Subtle effects were not detected for doses below the dose that blocked ovulation. The C₃H An/f mouse was investigated for the carcinogenic action of MGA. Data derived from life-span mouse studies indicated that MGA was not a carcinogen per se, even though massive doses (0.5 mg/mouse/day) could influence mammary tumor development in some instances; this effect is attributed to the influence of MGA on the general hormonal milieu. MGA increased the serum prolactin concentration of mice fed MGA at a daily rate of 0.2-0.8 mg. Tissue residue data demonstrated that MGA was located in the fat concentrations < 25 ppb in all cattle investigated and < 1 ppb in about 90% of the commercial feedlot cattle investigated. Based on the relationship between MGA residues in cattle, doses that might be biologically active in the human, and human consumption, it is estimated that at least 5-1,100 pounds of meat products would have to be consumed daily to achieve a dose of 0.7 mg, the predicted minimal effect dose in humans. (54 refs.)

77-5523 **Effect of Progestogens on the Liver: Comparative Evaluation in Rodents, Dogs, and Monkeys**

in Long-term Toxicity Studies (Meeting Abstract). (Eng.) Schuppler, J. (Dept. Experimental Toxicology, Res. Lab. Schering AG, Berlin, W. Germany); Gunzel, P.; El Etreby, M. F. *J Toxicol Environ Health* 3(1/2): 370-371; 1977. (3 refs.)

77-5524 **Cervicovaginal and Mammary Gland Abnormalities in Old BALB/cCRGL Mice Treated Neonatally with Progesterone (Meeting Abstract).** (Eng.) Jones, L. A. (Dept. Zoology, Univ. California, Berkeley, CA 94720); Bern, H. A.; Wong, L. M. *J Toxicol Environ Health* 3(1/2): 360-361; 1977. (no refs.)

77-5525 **Epidemiological Relationship Between Steroid Hormones and Liver Lesions.** (Eng.) Mahboubi, E. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB 68105); Shubik, P. *J Toxicol Environ Health* 3(1/2): 207-218; 1977.

In the past 3 yr, > 140 cases of benign liver cell adenomas have been reported in oral contraceptive users. Because > 40% of the cases presented with sudden pain, shock, and life-threatening hemorrhage (8% fatality rate), an epidemiologic study was initiated in Nebraska. Twenty cases of liver tumors in oral contraceptive users (median age 29.4 yr) were identified. The lesions included 10 benign adenomas, 4 hepatocellular carcinomas, 3 focal nodular hyperplasias, 1 spontaneous rupture of the liver, and 1 hamartoma. Of the 17 patients for whom information about pill type was available, 16 had taken a mestranol combination pill and 1 had taken an ethynylestradiol combination. (16 refs.)

77-5526 **Problems in Evaluating Chronic Toxicity of Contraceptive Steroids in Dogs.** (Eng.) Weikel, J. H. (Dept. Pathology and Toxicology, Mead Johnson Res. Center, Evansville, IN 47721); Nelson, L. W. *J Toxicol Environ Health* 3(1/2): 167-177; 1977.

Long term use of norethindrone and ethynylestradiol, a sequential regimen of dimethisterone and ethynylestradiol, and daily use of megestrol acetate were studied in female dogs. The steroids induced endometrial hyperplasia and pyometra in dogs receiving some preparations and caused mammary changes, including adenocarcinoma, in dogs receiving other preparations. Since the latter have not been observed in monkeys or rats, the relevance of these changes for extrapolation to humans is uncertain. (10 refs.)

77-5527 **Basaloid Adenomas of the Mammary Gland in Beagle Dogs Administered Investigational Con-**

traceptive Steroids. (Eng.) Kwapien, R. P. (Dept. Veterinary Pathology, Armed Forces Inst. Pathology, Washington, DC 20306); Giles, R. C.; Geil, R. G.; Casey, H. W. *J Natl Cancer Inst* 59(3): 933-939; 1977.

A series of 82 basaloid adenomas (BA) occurred in the mammary glands of 29/171 female beagle dogs given oral contraceptive steroids for 5-7 yr, starting at 10-14 mo of age. These BA were observed in 29/85 of the dogs developing mammary tumors, and they comprised about 10% of the mammary nodules recorded during the study. They resembled basal cell adenomas of the human salivary glands, human cutaneous basal cell tumors, and certain human and canine adnexal tumors. The BA were seen in dogs given ethynone (1.0 mg/kg/day), ethynone + mestranol (20:1; 1.05 mg/kg/day), WY-4355 + mestranol (20:1; 0.084, 0.42, and 1.05 mg/kg/day), or anagestone acetate + mestranol (20:1; 0.44 and 1.10 mg/kg/day) for 5 yr, but not in those given mestranol alone (0.02 or 0.05 mg/kg/day for 7 yr). The incidence of BA was highest in dogs given WY-4355 + mestranol (8/16 at 1.05 mg/kg/day) or anagestone acetate + mestranol (6/13 at 1.10 mg/kg/day). The observed BA appeared to be benign proliferative lesions, usually ≤ 1 cm in diameter, and they were present for as long as 45 mo without signs of infiltration or metastases. (39 refs.)

77-5528 The Influence of Stress and Stress Hormones on the Transplantability of a Nonimmunogenic Syngeneic Murine Tumor. (Eng.) Peters, L. J. (Section Experimental Radiotherapy, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX 77030); Kelly, H. *Cancer* 39(4): 1482-1488; 1977.

Quantitative transplantation assays of a syngeneic murine adenocarcinoma were used to investigate the effects of stress hormones on tumor take in CBA/Ht mice. Cortisol, injected ip 1 hr before and 3 hr after the tumor cells, caused a dose-dependent reduction of the TD_{50} (number of tumor cells required for 50% takes) by a factor of 4 at a total dose 4 $\mu\text{g/g}$ to a factor of 68 at 400 $\mu\text{g/g}$. ACTH at 0.2 IU/day for 9 days reduced the TD_{50} 2.5 fold, indicating that the peak glucocorticoid level achieved, rather than its duration, was of greater significance. Adrenaline, although much less effective than cortisol, produced an eightfold reduction in the TD_{50} at its max tolerable dose (4 $\mu\text{g/g}$). The effect of cortisol simulated that of whole-body (^{60}Co) irradiation (WBI, 147-153 rads/min). Although both these agents depress immune reactivity, evidence is presented that immunological mechanisms are not responsible for their effect. WBI constitutes a systemic stress, and the demonstration that laparotomy could also reduce the TD_{50} for this tumor suggested that both might act via endogenous glucocorticoids. However, the failure of prior total adrenalectomy of mice to abrogate the effect of WBI or laparotomy indicated that stress hormones were not essential intermediaries. It is concluded that stress hormones, especially glucocorticoids, and stressful procedures acting in-

dependently of stress hormones can facilitate tumor transplantation. (21 refs.)

77-5529 A Multicentre Study of Rauwolfia Derivative and Breast Cancer. (Eng.) Christopher, L. J. (Dept. Pharmacology and Therapeutics, Univ. Dundee, Dundee, Scotland); Crooks, J.; Davidson, J. F.; Erskine, Z. G.; Gallon, S. C.; Moir, D. C.; Weir, R. D. *Eur J Clin Pharmacol* 11(6): 409-417; 1977.

A study was made to ascertain whether there was an association between the use of rauwolfia derivatives and the development of breast cancer. The records (1969-1974) of 646 female patients discharged from Scottish hospitals with a confirmed diagnosis of breast cancer were examined and compared with the records of two matched control groups: one with cancer other than breast cancer and one with nonmalignant disorders. Data were also compared with those of several US cities. There was a lack of agreement of results from different centers. Most studies revealed a connection between hypertension and breast cancer. Rauwolfia drug exposure appeared to be marginally greater in the breast cancer group. It was not possible to disprove an association between rauwolfia derivatives and breast cancer. However, the findings suggest that if there is a risk, it must be extremely small. (8 refs.)

77-5530 Absence of Uterine Neoplasia in Patients on Bromocriptine. (Eng.) Besser, G. M. (Dept. Endocrinology, St. Bartholomew's Hosp., London EC1A 7BJ, England); Thorner, M. O.; Wass, J. A.; Doniach, I.; Cant, G.; Curling, M.; Grudzinskas, J. G.; Setchell, M. E. *Br Med J* 2(6091): 868; 1977.

Because of reports of endometrial neoplasia, metaplasia or hyperplasia in rats receiving bromocriptine, endometrial and cervical specimens were examined in 88 women who had bromocriptine treatment for up to 6 yr. No cytological or histological evidence of abnormalities was found in any of the women. (4 refs.)

77-5531 Some Biochemical Changes Associated with Nafenopin-induced Liver Growth in the Rat. (Eng.) Levine, W. G. (Dept. Pharmacology, Albert Einstein Coll. Medicine, Bronx, NY 10461); Ord, M. G.; Stocken, J. A. *Biochem Pharmacol* 26(10): 939-942; 1977.

Ornithine decarboxylase (OD) activity, DNA synthesis, and amino acid uptake were examined in rat liver following single po or ip dose (200 mg/kg) of the hypolipidemic drug nafenopin, or 2-methyl-2[p-(1,2,3,4-tetrahydronaphthyl)phenoxy]propionic acid. A weighed amount of food was given to male Wistar rats each day, and the amount consumed was determined. Liver wt increased for 3 days and

turned to normal in 6 days, but at no time did food consumption differ from that of controls. Liver protein concentrations were unchanged, but DNA concentration decreased slightly. OD activity, DNA synthesis, and amino acid uptake were markedly stimulated. After ip nafenopin, the onset of these responses was more rapid and the degree of induction greater than they were after po nafenopin. Since OD and DNA synthesis increased at the same time after po nafenopin, there is some doubt as to whether induction of OD is obligatory prior to DNA synthesis. However, the results do support a role for increased amino acid uptake in the prereplicative phase of liver growth. The po/ip difference in induction rates of these parameters may be attributable to a slow rate of absorption of po nafenopin in the rat. The possibility that nafenopin causes hepatic necrosis has not been confirmed in previous experiments ranging from 2 days to several weeks. The stimulation of liver growth, therefore, should be considered an adaptive rather than a toxic response. (41 refs.)

5532 **Formation of Functional Striated Muscle Cells from Non-Muscle Precursors Following Treatment with 5-Aza-cytidine (Meeting Abstract).** (Eng.) Continides, P. G. (Dept. Medical Biochemistry, Univ. Stellenbosch, Stellenbosch, Republic of South Africa); Jones, P. S. *Afr J Sci* 73(6): 187; 1977. (3 refs.)

5533 **A Novel Mixed Hepatocyte-Fibroblast Culture System and Its Use as a Test for Metabolism-Mediated Cytotoxicity.** (Eng.) Fry, J. R. (Dept. Biochemistry, Univ. Surrey, Guildford, Surrey, GU2 5XH, England); Bridges, J. W. *Biochem Pharmacol* 26(10): 9-973; 1977.

A mixed hepatocyte-fibroblast culture system was used to study cyclophosphamide metabolism. The toxicity of the compound to fibroblasts was markedly enhanced upon co-cultivation with rat hepatocytes. 2-Diethylaminoethyl-2,2-bis(4-phenylvalerate) HCl reduced this cytotoxicity. A dose-response curve for cyclophosphamide toxicity was constructed. This culture system can be used for other cytotoxicity studies. (23 refs.)

5534 **Transformation of Mammalian Cell Cultures by Antischistosomal Drugs (Meeting Abstract).** (Eng.) Kos, W. L. (Univ. Maryland, College Park, MD 20742). *Diss Abstr Int [B]* 38(2): 515; 1977. (no refs.)

5535 **Selective Inhibition of the 3' to 5' Exonuclease Activity Associated with DNA Polymerases: A Mechanism of Mutagenesis.** (Eng.) Byrnes, J. J. (Dept. Medical Veterans Admin. Hosp., Miami, FL 33152); Downey,

K. M.; Que, B. G.; Lee, M. Y.; Black, V. L.; So, A. G. *Biochemistry* 16(17): 3740-3746; 1977.

A study was conducted to establish that the mutagenicity and carcinogenicity of 6-mercaptopurine (6-MP) are due to selective inhibition of the 3' to 5' exonuclease activity associated with DNA polymerases. The results indicate that the 3' to 5' exonuclease activities of both mammalian and bacterial DNA polymerases can be selectively inhibited by nucleoside 5'-monophosphates, but polymerase activity is not affected. Neither mammalian nor bacterial exonuclease was inhibited by nucleosides, 3'-nucleotides, or cyclic 3', 5'-nucleotides. The selective inhibition of the 3' to 5' exonuclease activity of the DNA polymerases by 5' nucleotides suggests that these compounds may be mutagenic, since continued DNA synthesis while the proofreading exonuclease was inhibited would lead to a higher frequency of misincorporation and, thus, to a higher incidence of mutation. (38 refs.)

77-5536 **Effect of Tumor Promoting Agents on Mutation Frequencies in Cultured V79 Chinese Hamster Cells.** (Eng.) Lankas, G. R. (Dept. Environmental Health, Univ. Cincinnati, Cincinnati, OH 45267); Baxter, C. S.; Christian, R. T. *Mutat Res* 45(1): 153-156; 1977.

Phorbol and 12-O-tetradecanoylphorbol-13-acetate (TPA) were tested for their effects on chemically induced ouabain-resistant mutations in Chinese hamster V79 cells. When added to the culture medium 42 hr after the mutagens N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) or methylazoxymethanol acetate (MAM), the two phorbol compounds (each 10 µg) increased the recovery of ouabain-resistant mutants without enhancing the cytotoxic effects of MNNG or MAM. Phorbol was less effective than TPA in enhancing mutant recovery, and the effect of TPA was greatest at the highest mutagen doses (1.5 µg/ml MNNG and 24 µg/ml MAM). The data suggest that phorbol compounds can modify gene expression and that mutagenesis is an initial event in carcinogenesis. (14 refs.)

77-5537 **Effect of a Tumor Promoting Agent on Mutation Frequency in Chinese Hamster Cells In Vitro (Meeting Abstract).** (Eng.) Lankas, G. R. (Dept. Environmental Health, Univ. Cincinnati, Cincinnati, OH 45221). *Clin Res* 25(4): 634A; 1977. (no refs.)

77-5538 **Qualitative and Quantitative Separation of a Series of Phorbol-Ester Tumor Promoters by High-Pressure Liquid Chromatography.** (Eng.) Berry, D. L. (Biology Div., Oak Ridge Natl. Lab., Post Office Box Y, Oak Ridge, TN 37830); Lieber, M. R.; Fischer, S. M.; Slaga, T. J. *Cancer Lett* 3(3-4): 125-132; 1977.

A rapid and efficient method is described for the separation and quantitation of 12-O-tetradecanoylphorbol-13-acetate (TPA) and its potential metabolites, and a series of phorbol diesters, by high-pressure liquid chromatography (HPLC) using a microparticulate silica-acid column and gradient elution. The ability to resolve TPA, 12-O-hexadecanoylphorbol-13-acetate (HPA), phorbol dibenzoate, phorbol dibutylate, phorbol diacetate, 4-O-methyl-TPA, 20-oxo-TPA, and phorbol was necessary to check the purity of the syntheses of these compounds and to check autooxidation of the esters on standing. All the esters were found to be at least 99% pure. Spectrophotometric determination at 232 nanometers allowed detection sensitivities of 0.05 μ g TPA. When 3 H-TPA was applied to mouse skin for 24 hr, most of the tritiated product recovered was TPA. Since only limited metabolism of TPA occurred the data indicate that metabolic activation of TPA is not essential for tumor promotion. (21 refs.)

- 77-5539 **Effects of Promoters on DNA Synthesis in C3H/10T1/2 Mouse Fibroblasts.** (Eng) Peterson, A. R. (LAC-USC Cancer Center, Cancer Res. Building, 1303 N. Mission Rd., Los Angeles, CA 90033); Mondal, S.; Brankow, D. W.; Thon, W.; Heidelberger, C. *Cancer Res* 37(9): 3223-3227; 1977.

Two-stage carcinogenesis was studied in cultured C3H/10T1/2 mouse embryo fibroblasts. The cultures were first treated with 0.1 or 0.25 μ g 3-methylcholanthrene (3-MC), followed either immediately or after 5 days with 0.1 μ g 12-O-tetradecanoyl-phorbol-13-acetate (TPA). Growth curves suggested that TPA delayed the onset of logarithmic growth; but when growth resumed, the doubling time was not significantly different from control cells. In addition to TPA, treatment of the log phase of growth with phorbol didecanoate or 4 α -phorbol didecanoate also produced a transient inhibition of DNA synthesis with a max at 12 hr after treatment. Doubling time after recovery was also normal for these promoters. Phorbol did not produce these effects, suggesting that the inhibition was associated with promotion. Although TPA treatment during stationary phase resulted in a two- to three-fold increase in DNA synthesis, treatments spanning log and stationary phases were necessary for promotion. (29 refs.)

- 77-5540 **Fluocinolone Acetonide: A Potent Inhibitor of Mouse Skin Tumor Promotion and Epidermal DNA Synthesis.** (Eng.) Schwarz, J. A. (Rutgers Univ. Medical Sch., Rutgers Medical Sch., New Brunswick, NJ 08901); Viaje, A.; Slaga, T. J.; Yuspa, S. H.; Hennings, H.; Lichti, U. *Chem Biol Interact* 17(3): 331-347; 1977.

The relationship between inhibition of tumor promotion and inhibition of DNA synthesis was examined using fluocino-

lone acetonide (FA) and flucolorolone acetonide (FC). Female Charles River CD-1 mice were treated with 200 nanomole of 7,12-dimethylbenz[a]anthracene (DMBA); 1 wk later, tumor promotion was begun with 2 μ g of 12-O-tetradecanoylphorbol-13-acetate (TPA). FA and FC were dissolved in TPA and applied topically. FA was used in doses of 10, 1, 0.1, 0.01, and 0.001 μ g; FC was used in doses of 10, 1, and 0.1 μ g. FA and FC were found to be much more potent inhibitors of TPA-induced tumor promotion in mouse skin than dexamethasone. Simultaneous doses of either 10, 1, or 0.1 μ g FA and 2 μ g TPA resulted in an almost complete inhibition of tumor promotion; the 1 μ g dose was most effective. Doses of 0.01 and 0.001 μ g FA resulted in inhibition of 82% and 15%, respectively. In general, as the dose was increased, the tumor latency period increased. Both 10 and 1 μ g doses of FC and FA in TPA were effective inhibitors; but the 1 μ g dose of FC resulted in only 62% inhibition compared to > 95% for FA. Further studies indicated that FA's effect was reversible and restricted to the promotion phase. FA had a greater effect on G-1 than on S-phase cells. The ability to inhibit tumor promotion is apparently related to inhibition of DNA synthesis. (42 refs.)

- 77-5541 **Metabolism of Naphthalene by *Cunninghamella elegans*.** (Eng) Cerniglia, C. E. (Dept. Microbiology, Univ. Texas at Austin, Austin, TX 78712); Gilson, D. T. *Appl Environ Microbiol* 34(4): 363-370; 1977.

When *Cunninghamella elegans* was grown on Sabourau dextrose broth in the presence of naphthalene, six metabolites were formed. Each product was isolated and identified by conventional chemical techniques. The major metabolites were 1-naphthal (67.9%) and 4-hydroxy-1-tetralone (16.7%). Minor products isolated were 1,4-naphthoquinone (2.8%), 1,2-naphthoquinone (0.2%), 2-naphthol (6.3%), and *trans*-1,2-dihydroxy-1,2-dihydronaphthalene (5.3%). *C. elegans* oxidized both 1-naphthol and 1,4-naphthoquinone to 4-hydroxy-1-tetralone. The results suggest that *C. elegans* oxidizes naphthalene by a sequence of reactions similar to those reported for the mammalian metabolism of this hydrocarbon. (43 refs.)

- 77-5542 **The Apparent Ubiquity of Epoxide Hydratase in Rat Organs.** (Eng.) Oesch, F. (Section on Biochemical Pharmacology, Inst. Pharmacology, Univ., Obere Zahlbacher Strasse 67, D-6500, Mainz, W. Germany); Glatt, H.; Schmassmann, H. *Biochem Pharmacol* 26(7): 603-607; 1977.

Epoxide hydratase (EH) was assayed in 26 organs of Sprague Dawley rats and 6 organs of NMRI mice, using tritiated benzo(a)pyrene 4,5-oxide (BPO) as the enzyme substrate. Of the tissues tested, EH activity was absent only in blood. In the rat, the specific EH activities in each tissue diminished in the

Following order: liver > testis > kidney > lung > intestine = skin. In the mouse, a different hierarchy was seen: testis > liver > lung > skin > kidney > intestine. Although pre-treatment of rats with Arochlor 1254 increased liver EH activity by 75%, the EH activity in 13 extrahepatic tissues was not significantly changed. When styrene oxide was used as a substrate for EH, the relative specific activities of rat liver, kidney, lung, and testis were similar to those with BPO as substrate. This suggests that a single enzyme is responsible for the hydration of both substrates in these tissues. (25 refs.)

77-5543 Hydration of Arene and Alkene Oxides by Epoxide Hydrase in Human Liver Microsomes.

(Eng.) Kapitulnik, J. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche, Incorporated, Nutley, NJ 07110); Levin, W.; Lu, A. Y.; Morecki, R.; Dansette, P. M.; Jerina, J. M.; Conney, A. H. *Clin Pharmacol Ther* 21(2): 158-165; 1977.

A comparative hydration of styrene 7,8-oxide, octene 1,2-oxide, naphthalene 1,2-oxide, phenanthrene 9,10-oxide, benzo(a)anthracene 5,6-oxide, 3-methylcholanthrene 11,12-oxide, dibenzo(a,h)-anthracene 5,6-oxide, benzo(a)pyrene (BP) 4,5-oxide, BP 7,8-oxide, BP 9,10-oxide, and BP 11,12-oxide to their respective dihydrodiols was investigated in microsomes from nine human autopsy livers. Appreciable epoxide hydrase activity was observed in the human liver specimens; its substrate specificity was similar to that of epoxide hydrase in rat liver microsomes. Phenanthrene 9,10-oxide was the best substrate for the human and rat epoxide hydrolases, dibenzo(a,h)-anthracene 5,6-oxide and BP 11,12-oxide were the poorest substrates. When the relationship between metabolic rates of the different substrates in the different livers was studied by plotting the enzyme activity with one substrate against the enzyme activity with a second substrate in each of the nine livers, excellent relationships were observed between the epoxide hydrase activities for all combinations. Large differences in epoxide hydrase activity were observed among the nine livers studied. It is possible that epoxide hydrase was induced in some of the human livers studied, especially in those from subjects who had been treated chronically with drugs that are inducers of microsomal enzymes. The results suggest the presence in human liver of a single epoxide hydrase with broad substrate specificity. (28 refs.)

77-5544 A Kinetic Study on the In Vitro Covalent Binding of Polycyclic Hydrocarbons to Nucleic Acids Using Epidermal Homogenates as the Activating System. (Eng.) Slaga, T. J. (Biol. Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Buty, S. G.; Thompson, S.; Bracken, M.; Viaje, A. *Cancer Res* 37(9): 3126-3131; 1977.

A possible correlation between the tumor-initiating ability of

several polycyclic aromatic hydrocarbons (PAH's) and their ability to bind covalently to DNA in an epidermal homogenate was examined. Epidermis was isolated from the skins of CD-1 mice treated topically with the corresponding PAH 18 hr before sacrifice. The binding of the various PAH's to DNA correlated with their tumor-initiating ability at all time points examined. Initially, the binding of 3-methylcholanthrene (3-MC) was linear, although a leveling off occurred with increased concentrations of substrate, enzyme, DNA, and NADPH. Covalent binding of 3-MC and benzo(a)pyrene (BP) to DNA by an NADPH-dependent epidermal homogenate was linear for 90 min, after which it leveled off. A second addition of NADPH increased DNA binding linearly for 90 additional minutes. At 12 hr after induction with the corresponding unlabeled PAH, the specific activities of PAH binding to DNA by the epidermal homogenates all peaked in the order 7,12-dimethylbenz(a)anthracene (DMBA) 3-MC > BP > dibenz(a,h)anthracene > dibenz(a,c)anthracene. Except for DMBA, all these PAH's have a strong need for NADPH. The reaction of BP with nucleic acids seems to occur predominantly with guanine residues. The specific activity of BP binding to the various nucleic acids was polyguanylic acid > polyadenylic acid > yeast RNA > DNA. (49 refs.)

77-5545 A Bacteriophage System for Screening and Study of Biologically Active Polycyclic Aromatic Hydrocarbons and Related Compounds. (Eng.) Hsu, W. T. (Franklin McLean Memorial Res. Inst., Dept. Biochemistry, Univ. Chicago, Chicago, IL 60637); Harvey, R. G.; Lin, E. J.; Weiss, S. B. *Proc Natl Acad Sci USA* 74(4): 1378-1382; 1977.

The use of bacteriophages to screen potentially carcinogenic polycyclic aromatic hydrocarbons was reexamined. A modification of the original assay procedure made it possible to distinguish between aromatics that can inactivate infectious nucleic acids directly and those requiring metabolic activation by *Escherichia coli* spheroplasts. Thirty-one derivatives of benz(a)anthracene, benzo(a)pyrene (BP), 7,12-dimethylbenz(a)anthracene, and phenanthrene were synthesized and screened. Of these derivatives (\pm)-anti-benzo(a)pyrene-7,8-diol-9,10-epoxide was the most effective inhibitor of infectious phage nucleic acid. Both the (+) and (-) isomers were equally active in this regard. These findings agree with the suggestion that BP-diolepoxide is the most carcinogenic polycyclic aromatic hydrocarbon. The sensitivity of infectious nucleic acid-spheroplast systems may be further enhanced by preincubating the hydrocarbons with mammalian extracts and by using certain bacterial mutants deficient in DNA excision repair. (32 refs.)

77-5546 Effect of Carbon Tetrachloride on α -Ketoglutarate Dehydrogenase and Succinate

Dehydrogenase Activity in Liver Mitochondria of Rats Given Polycyclic Hydrocarbons. (Ukr.) Gub'skii, Iu. I. (O. O. Bogomolets Medical Inst., Kiev, USSR); Pradii, T. P. *Ukr Biokhim Zh* 49(4): 26-30; 1977.

The effects of 3-methylcholanthrene (3-MC), dibenzo(a,h)anthracene (DBA), and actinomycin D on the action of carbon tetrachloride (CCl₄) on liver mitochondrial α -ketoglutarate dehydrogenase (KGD) and succinate dehydrogenase (SDH) activities were studied in male albino rats. When administered alone ip, CCl₄ inhibited KGD and SDH considerably (47% and 42%, respectively). DBA and 3-MC, administered ip 24 hr before CCl₄, decreased KGD activity even more, by 56% and 58%, respectively. 3-MC decreased SDH activity by 55%. 3-MC and DBA reduced the LD50 of CCl₄ to 0.12 ml/100 g and 0.13 ml/100 mg, respectively, from a value of 0.29 ml/100 g. Actinomycin D, administered together with 3-MC or DBA, prevented the 3-MC- and DBA-induced enhancement of the hepatotoxicity of CCl₄. (17 refs.)

77-5547 Effect of Polycyclic Hydrocarbons on the Ultrastructure and Enzymatic Properties of Hepatocytes in Rats Poisoned with Carbon Tetrachloride. (Rus.) Gub'skii, Iu. I. (Kiev Medical Inst., Kiev Scientific-Res. Inst. Clinical and Experimental Surgery, Kiev, USSR); Sil'chenko, V. P.; Pokras'on, M. M. *Dopov Akad Nauk Ukr RSR (Ser B)* (1): 66-69; 1977.

Histochemical, ultrastructural, and biochemical changes in the rat liver were studied 2 and 20 hr after exposure to carbon tetrachloride (CCl₄) subsequent to the administration (20 hr earlier) of 3-methylcholanthrene and dibenz(a,h)anthracene. The two polycyclic hydrocarbons enhanced the destructive effect of CCl₄ on the liver. The changes in liver architecture and hepatocyte ultrastructure were more severe, the extent of necrosis increased, and the bioenergetic processes in the mitochondria were affected markedly. Potentiation of the hepatotoxic effect of CCl₄ by 3-methylcholanthrene and dibenz(a,h)anthracene may be connected with activation of microsomal cytochrome P-488 biosynthesis, which results in highly toxic CCl₄ metabolites (free radicals). (13 refs.)

77-5548 The Effects of Benzoflavones on Polycyclic Hydrocarbon Metabolism and Skin Tumor Initiation. (Eng.) Slaga, T. J. (Cancer and Toxicology Program, Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Thompson, S.; Berry, D. L.; Digiovanni, J.; Juchau, M. R.; Viaje, A. *Chem Biol Interact* 17(3): 297-312; 1977.

A study was made of the effects of benzoflavone (BF) on (1) skin tumor initiation in female CD-1 mice by topical administration of various polycyclic hydrocarbons and (2) epidermal aryl hydrocarbon hydroxylase (AHH) levels. Topically administered 7,8-BF was a potent inhibitor of skin tumors initiated by 3-methylcholanthrene and 7,12-

dimethylbenzanthracene (DMBA), but not of tumors initiated by 7-hydroxymethyl-12-methylbenz(a)anthracene. When 100 μ g 7,8-BF was administered 5 min prior to DMBA, mice in an experimental group, 90% of all tumors were inhibited after 30 wk of promotion (compared to the number of tumors in controls not given 7,8-BF). 5,6-BF also inhibited tumor formation, but less effectively. Epidermal AHH was increased by 5,6-BF administration and unaltered or slightly inhibited by 7,8-BF. Both substances inhibited the in vivo epidermal AHH activity. It is suggested that the inhibition of skin tumor initiation by 7,8-BF and 5,6-BF is related to their ability to inhibit the formation of electrophilic metal complexes of the initiating polycyclic hydrocarbons. (36 refs.)

77-5549 Polynuclear Aromatic Hydrocarbons in Marine Tissues. (Eng) Pancirov, R. J. (Analytical and Information Div., Exxon Res. and Engineering Co., Linden, NJ 07036); Brown, R. A. *Environ Sci Technol* 11(10): 989-992; 1977.

The concentrations of benz(a)anthracene (BA), benzo(a)pyrene (BP), pyrene, methylpyrene, and other individual polynuclear aromatic hydrocarbons were investigated in shell- and finfish from waters off the coast of Massachusetts, New York, New Jersey, Virginia, and Texas, and from a lake in Canada. All of the BA levels were < 2 ppb, except for a level of 8 ppb in oysters from Long Island Sound. All concentrations of BP were < 1.5 ppb, except for levels of 2 ppb in oysters from Long Island Sound and flounder from the Atlantic Ocean and 3 ppb in crabs from Raritan Bay. All pyrene levels were < 1 ppb except for levels of 58 ppb in oysters from Long Island Sound, 12 ppb in clams from Connecticut, 6 ppb in crabs from Raritan Bay, 2 ppb in flounder from the Atlantic, and 4 ppb in mussels from Massachusetts. Methylpyrene levels were all < 2.5 ppb except for levels of 11 ppb in oysters from Long Island Sound. Compared with other foodstuffs, neither shell- nor finfish showed unusually high amounts of polynuclear aromatics, and lower concentrations were found in fish than in many other foods. (19 refs.)

77-5550 Transplacental Effect of Benzo(a)pyrene and Pyrene. (Rus.) Nikonova, T. V. (Dept. Carcinogenic Agents, Oncological Res. Center, Acad. Med. Sciences USSR, Moscow, USSR). *Biull Eksp Biol Med* 84: 88-91; 1977.

The transplacental and direct carcinogenic effects of benzo(a)pyrene (BP) were studied in mothers and offspring (C57BL line mice) 1 yr after sc application of 4-, 6-, 12-mg doses of BP on the 18th-19th days of pregnancy. In line A offspring, 6 mg proved to be the most effective dose in inducing pulmonary adenomas in 76.8% of all mice (12.3% in controls). Increasing the dose to 12 mg failed to intensify the carcinogenic effect of BP. At a dose of 6

induced lung adenoma in 27.1% of C57BL mice (vs 2.3% controls), mammary gland tumors in 23.5%, and liver tumors in 16.7%. Unlike A line mice, the incidence of lung tumors in C57BL mice was higher among females than among males. The incidence of tumors (at the injection site, lungs, and mammary glands) in the mothers was always lower than that in their offspring. (7 refs.)

5551 **Effect of Benzene and 3,4-Benzopyrene on Transcription in Nuclei and Chloroplasts.** (Rus.) Mishidze, S. V. (Inst. Plant Biochemistry, Acad. Sciences Georgian SSR, Tbilisi, USSR); Dzhokhadze, D. I. *Dokl Akad Nauk SSSR* 232(1): 233-235; 1977.

To determine the effect of aromatic hydrocarbons on the endogenous synthesis of RNA, isolated nuclei and chloroplasts from the leaves of pea plants and nuclei from the rat liver were incubated with benzene (B) and 3,4-benzopyrene (BP). At a ratio of 25 μ l B:40-120 μ g DNA, B increased RNA synthesis by 11%-52% in the nuclei of the pea leaves; in the chloroplasts, at a ratio of 25 μ l B:8-32 μ g DNA, RNA synthesis was inhibited 11%-44%. BP induced RNA synthesis in both plant (32%-144%) and animal (28%-63%) nuclei. (4 refs.)

5552 **Polycyclic Aromatic Hydrocarbon Concentrations and Carcinogenicity of Extracts from Soot Generated by Heating Equipment.** (Rus.) Khesina, A. Ia. (Experimental and Clinical Oncology, Acad. Medical Sciences USSR, Moscow, USSR); Gaevaia, T. Ia.; Linnik, A. *Ig Sanit* (8): 107-109; 1977.

Generated during the combustion of wood and brown coal was analyzed for polycyclic aromatic hydrocarbons (PAH), and the carcinogenicity of benzene extracts of the and of pure benzo(a)pyrene (BP) was studied in F₁(C57BL x CBA) hybrid mice. The animals were given five sections of soot extracts or BP (total dose 0.22 mg) in 8 wk. The incidence was highest and the latency time shortest in the group treated with pure BP; tumor mortality after the first week was 80%, and the first tumors appeared after 15 weeks. Tumor mortality (17%) and the latency time (not stated) were about the same in groups treated with extracts of two different soots. The levels of BP and other PAH were about 10 times higher in wood soot than in coal soot. In wood soot, the concentrations of all PAH were within the same order of magnitude, but in coal soot the concentrations of the heavy PAH were about the one-tenth of those with three to four benzene rings. In both soots, the concentration of BP was lower than that of the other PAH with five to six benzene rings. Soot extracts contain not only carcinogens but also substances that inhibit the carcinogenic process as a result of inhibition of the metabolic degradation of carcinogenic substances or by direct inhibiting action. (4 refs.)

77-5553 **Characterization of Benzo[a]pyrene Hydroxylase of Trout Liver.** (Eng.) Ahokas, J. T. (Dept. Pharmacology, Univ. Oulu, SF-90 220 Oulu 22, Finland); Pelkonen, O.; Karki, N. T. *Cancer Res* 37(10): 3737-3743; 1977.

The benzo(a)pyrene hydroxylase activity of trout (*Salmo trutta lacustris*) liver microsomes required NADPH and O₂ and was inhibited by CO. Of inhibitors tested in this system, typical inhibitors of 3-methylcholanthrene-induced cytochrome P-448 were effective. Cytochrome P-450, found in the microsomes in concentrations of up to 0.40 nanomoles/mg protein, had a max absorbance at 450.6 nanometers when in the reduced form. (28 refs.)

77-5554 **Role of Sulfhydryl Groups in the Hydroxylation of Benzo[a]pyrene by Purified Rat and Rabbit Cytochrome P-448.** (Eng.) Kawalek, J. C. (Frederick Cancer Res. Center, Litton Bionetics, Inc., Frederick, MD 21701); Levin, W.; Ryan, D.; Lu, A. Y. *Arch Biochem Biophys* 183(2): 732-741; 1977.

The effects of several sulfhydryl reagents on the hydroxylation of benzo[a]pyrene (BP) was investigated using rat and rabbit cytochromes P-448. The liver microsomes from both animals contained seven free sulfhydryl groups per mole of enzyme. Differential inhibition of hydroxylation by the cytochromes from the two sources was exhibited after enzyme modification with various sulfhydryl reagents. Thus sulfhydryl groups may or may not have an essential role in catalysis of BP hydroxylation. (49 refs.)

77-5555 **Liver Microsomal Electron Transport Systems. Properties of a Reconstituted, NADH-mediated Benzo(a)pyrene Hydroxylation System.** (Eng.) West, S. B. (Dept. Biochemistry and Drug Metabolism, Hoffman-La Roche, Inc., Nutley, NJ 07110); Lu, A. Y. *Arch Biochem Biophys* 182(2): 369-378; 1977.

An enzyme system from rat liver microsomes that catalyzes the NADH-dependent hydroxylation of benzo(a)pyrene (BP) was reconstituted. The essential microsomal components of the NADH-dependent pathway was NADH-cytochrome b₅ reductase, cytochrome b₅, cytochrome P-448, and phosphatidylcholine. The effect of highly purified NADPH-cytochrome c reductase on this system was also examined. The results indicate an absolute requirement for cytochrome b₅ in one pathway of NADH-mediated BP hydroxylation. The optimum molar ratio of cytochrome b₅ to cytochrome P-448 in the reconstituted system was 1. There was no further effect with a higher concentration of cytochrome b₅. NADPH-cytochrome c reductase in combination with cytochrome P-448 and phosphatidylcholine also supported a low rate of NADH-dependent hydroxylation. When deoxycho-

late was not present, the hydroxylation rate via the cytochrome b₅-dependent pathway was only 19% of the rate in the presence of deoxycholate. The results indicate that the relative contribution of the pathway due to NADPH-cytochrome c reductase in combination with cytochrome P-448 and phosphatidylcholine to the total activity depends on the concentration of NADH used, since high concentrations of NADH can reduce NADPH-cytochrome c reductase. NADH may support the metabolism of a substrate by more than one pathway. (48 refs.)

- 77-5556 **Quantitation of Fibrinolytic Activity of Syrian Hamster Fibroblasts Using ³H-labeled Fibrinogen Prepared by Reductive Alkylation.** (Eng.) Barrett, J. C. (Div. Biophysics, Sch. Hygiene, Johns Hopkins Univ., Baltimore, MD 21205); Crawford, B. D.; Ts'o, P. O. *Cancer Res* 37(4): 1182-1185; 1977.

Tritium-labeled fibrinogen (specific activity 2.0×10^7 cpm/mg) was prepared by reductive alkylation and used as a substrate for detecting intracellular and extracellular fibrinolytic activity in cultures of benzo(a)pyrene-transformed Syrian hamster embryo cells. In cell-free assays, ³H-fibrinogen enabled the reliable quantitation of fibrinolytic activity in transformed cells. The elevated extracellular fibrinolytic activity of these cells, compared with normal cells, was also demonstrated with this substrate. The ease with which large quantities of ³H-fibrinogen with high specific activity and a long half-life can be prepared makes the substrate an attractive alternative to ¹²⁵I-labeled fibrinogen. (14 refs.)

- 77-5557 **Benzo(a)pyrene Carcinogenesis: A Biochemical Selection Mechanism.** (Eng.) Selkirk, J. K. (Carcinogenesis and Carcinogen Metabolism, Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830). *J Toxicol Environ Health* 2(6): 1245-1258; 1977.

Discussion is made of the metabolism of benzo(a)pyrene (BP) in several systems, in which the profile of BP metabolites produced was studied by high pressure liquid chromatography. The systems include rat, mouse, and hamster liver microsomes and disrupted and intact hamster embryo fibroblasts. The spectrum of metabolites produced was the same in all cases; however, major differences were seen in the relative amounts of particular products formed. In disrupted hamster embryo cells incubated with BP for 1 hr, the predominant products were phenols, and quinones were also evident. The predominant species following the incubation of intact cells for 24 hr were the 9,10-diol and the 7,8-diol; quinones were no longer seen. Thus, the particular metabolites observed depend upon the experimental conditions. This must be taken into account in con-

siderations of which species may be relevant to carcinogenesis in vivo. (20 refs.)

- 77-5558 **Hydroponic Growth of Crops in Solutions Saturated with [¹⁴C]Benzo(a)pyrene.** (Eng.) Blum, C. (Analytical and Information Div., Exxon Res. and Engineering Co., Linden, NJ 07036); Swarbrick, R. E. *J Agric Food Chem* 25(5): 1093-1096; 1977.

Green beans, cantaloupes, and cottonseeds were grown hydroponically in nutrient solution of ¹⁴C-labeled benzo(a)pyrene (BP) and analyzed by liquid scintillation counting techniques. BP did not translocate or concentrate in any of the crops tested. (4 refs.)

- 77-5559 **Effects of Benzo(a)pyrene on Monolayer Cultures of Normal and Malignant Mouse Liver Cells.** (Rus.) Budunova, I. V. (Lab. Chemical Carcinogenesis, Oncological Res. Center, Acad. Medical Sciences USSR, Moscow, USSR); Vainberg, R. M. *Biull Eksp Biol Med* 84(9): 346-349; 1977.

The effects of benzo(a)pyrene (BP: 0.1, 1, and 10 µg/ml) on monolayers of normal mouse embryonal hepatocytes and highly malignant ascitic hepatoma 22a were studied in vitro. When added in low concentrations, BP was metabolized 100% by the normal hepatocytes; the rate of metabolism was > 75% in 72 hr when 10 µg/ml BP was added. The hepatoma cells metabolized BP nearly as efficiently as the normal cells. Both cultures were highly sensitive to BP, which reduced the cell density of the culture considerably. At 10 µg/ml, BP suppressed mitosis completely in both cultures. The findings indicate that the in vivo resistance of hepatic tissue to BP is due to factors acting at the organ or organism level rather than at the cellular level. (12 refs.)

- 77-5560 **High Carcinogenicity of 2-Hydroxybenzo(a)pyrene on Mouse Skin.** (Eng.) Wislocki, P. G. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche, Inc., Nutley, NJ 07110); Chang, R. L.; Wood, A. W.; Levin, W.; Yagi, H.; Hernandez, O.; Mah, H. D.; Dansette, P. M.; Jerina, D. M.; Conney, A. H. *Cancer Res* 37(8, part 1): 2608-2611; 1977.

Benzo(a)pyrene (BP) and five isomeric phenols of BP were tested for carcinogenicity by the topical application of each compound (0.4 micromole/2 wk for 60 wk) to the backs of C57BL/6J mice. 1-, 3-, and 12-hydroxy-BP were noncarcinogenic, 11-hydroxy-BP was weakly carcinogenic, and 2-hydroxy-BP and BP were highly carcinogenic. Most of the

tors were squamous cell carcinomas. The results indicate that of the 12 possible isomers of hydroxy-BP, only the 2-methyl isomer is highly carcinogenic. (42 refs.)

5561 **Marked Differences in the Tumor-initiating Activity of Optically Pure (+)- and (-)-trans-7,8-dihydroxy-7,8-dihydrobenzo(a)pyrene on Mouse Skin.** (Eng.) Levin, W. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche, Inc., Nutley, NJ 07110); Wood, A. W.; Wang, R. L.; Slaga, T. J.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res* 37(8, part 1): 2721-2725; 1977.

A study was made of the ability of benzo(a)pyrene (BP) and optically pure (+)-trans-7,8-dihydroxy-7,8-dihydro-BP [(+)-DBP] and (-)-trans-7,8-dihydroxy-BP [(-)-DBP] to initiate skin tumors in female CD-1 mice. The order of mutagenic potency was (-)-DBP > BP >> (+)-DBP. When a single application of 50-200 nanomoles of the (-)-DBP enantiomer was applied to the backs of the mice, followed by repeated applications of promotor (12-O-tetradecanoyl phorbol-13-acetate), (-)-DBP proved to be 5 to 10 times more active than the (+)-DBP enantiomer. This is the first report of difference in carcinogenicity between optical enantiomers. (33 refs.)

5562 **Transformation of Normal Hamster Cells by Benzo(a)pyrene Diol-Epoxyde.** (Eng.) Mager, R. (Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel); Shoham, E.; Yang, S. K.; Gelboin, H. V.; Sachs, L. *Int J Cancer* 19(6): 814-817; 1977.

Determination was made of the transformation frequencies of normal hamster embryo cells treated either with benzo(a)pyrene (BP) or with one of six BP metabolites: the trans 4,5-diol, 9,10-dihydrodiols, BP-4,5-epoxide, and two stereoisomers of the non-K-region diol epoxides [r-7,t-8-dihydroxy-t-10-oxy-7,8,9,10-tetrahydro-BP (diol epoxide I) and r-7,6-8-dihydroxy-c-9,10-oxy-7,8,9,11-tetrahydro-BP (diol epoxide II)]. The trans 7,8-dihydrodiol was more active than the other dihydrodiols; ie, the percentage of transformed colonies after exposure to 3 µg/ml of materials was 0.9% with BP, 0.1% with trans-4,5-diol, 0.5% with trans-7,8-diol, and 0% with trans-9,10-diol. Diol epoxide I was the most active of the epoxides tested: the percentage of transformed colonies with 3 µg/ml of material was 0.1% with the 4,5-epoxide, 1.4% with diol epoxide I, and 0.2% with diol epoxide II. The results suggest that diol epoxide I is a major transforming metabolite of BP. (26 refs.)

5563 **The Metabolism of 4,5-Dihydro-4,5-dihydroxybenzo(a)pyrene by Short-term Organ**

Cultures of Hamster Trachea and Lung. (Eng.) Moore, B. P. (Dept. Biochemistry, Univ. Surrey, Guildford GU2 5XH, Surrey, England); Cohen, G. M.; Bridges, J. W.; Parke, D. V. *Biochem Soc Trans* 5(5): 1368-1370; 1977.

The metabolism of trans-4,5-dihydro-4,5-dihydroxybenzo(a)pyrene (4,5-dBAP) in short term organ cultures of hamster trachea or lung was investigated. 4,5-dBAP (0.4 to 1.0 µM) was added to 30 to 70 mg trachea or 200 mg lung and maintained for 16 hr before analysis. With incubations of 1 µM 4,5-dBAP, 93.4% of the radioactivity remained in the medium at the end of the tracheal culture; but only 65.7% remained after lung culture. Of this, 66.4% was ethyl acetate-soluble after tracheal culture and 34.1% after lung culture. A major peak of radioactivity was observed in this portion, corresponding to 4.5 and 10.7 picomole/min/g from lung and trachea, respectively. This metabolite may be the further metabolite of an epoxide that is involved in the carcinogenicity of 4,5-dBAP. The medium also contained a water-soluble radioactivity that was associated with glucuronide in the trachea and lung. The rate of glucuronide conjugation of 4,5-dBAP by lung was 14.0 picomole/min/g; the rate for trachea could not be accurately determined. This conjugate may be important in the detoxification of materials deposited in the trachea from particulate material in the urban atmosphere. (4 refs.)

77-5564 **Modification of Benzo(a)pyrene Metabolism with Microsomes by Addition of Uridine 5'-Diphosphoglucuronic Acid.** (Eng.) Nemoto, N. (Dept. Experimental Pathology, Cancer Inst., 1-37-1 Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan); Takayama, S. *Cancer Res* 37(11): 4125-4129; 1977.

The metabolism of benzo(a)pyrene (BP) by Wistar rat liver microsomes was examined in the presence and absence of uridine-5'-diphosphoglucuronic acid (UDPGA). BP metabolites were separated by high-pressure liquid chromatography. The normal chromatographic patterns of the metabolites were altered by the addition of UDPGA. At UDPGA concentrations at which the elutions of dihydrodiol components were unchanged, phenol and quinone elution profiles were selectively decreased. A UDPGA-induced decrease in the activities of microsomal mixed-function oxidases was observed in the aryl hydrocarbon hydroxylase assay. The decrease may have been due to formation of glucuronide conjugates with oxygenated BP metabolites, rather than to inhibition of the enzymes. These results suggest that glucuronidation may be important in BP detoxification. (32 refs.)

77-5565 **The Role of Microsomes and Nuclear Envelope in the Metabolic Activation of Benzo(a)pyrene**

Leading to Binding with Nuclear Macromolecules. (Eng) Pezzuto, J. M. (Dept. Biochemistry, Coll. Medicine and Dentistry New Jersey, New Jersey Medical Sch., Newark, NJ 07013); Lea, M. A.; Yang, C. S. *Canc Res* 37(9): 3427-3433; 1977.

The effect of added microsomes on benzo(a)pyrene (BP) binding to nuclear macromolecules was studied under a variety of conditions using male Long-Evans rats given a daily 25 mg/kg ip injection of 3-methylcholanthrene (3-MC) for 4 days. 3-MC treatment induced nuclear and microsomal cytochrome P-448 which has a higher aryl hydrocarbon hydroxylase (AHH) activity than the P-450 of control mice. A 30 min incubation of 3-MC nuclei with BP reduced the levels of BP binding when concentrations of 1 or 2 μ M were used. This inhibition was not observed with 30 μ M BP. When equal amounts of denatured microsomes were added, levels of binding were also reduced. It is suggested that physical binding of BP to microsomes reduced the quantity of BP available for metabolism by the nuclei. This resulted in a lower covalent binding of BP to nuclear macromolecules with the addition of denatured microsomes or with the addition of active microsomes when lower BP concentrations were used. Studies on the effect of length of time on incubation of MC nuclei, MC or denatured microsomes, 2 μ M BP and NADPH revealed that with short (2 to 8 min) incubation, the level of binding was greater when native 3-MC microsomes were included. This effect disappeared by 30 min incubation. With 2 μ M BP, 68% was bound to microsomes, 22% bound to nuclei, and 10% was in the supernatant. With NADPH added, the microsome-bound fraction was cut in half and the nuclei-bound fraction decreased to 14%; this was probably due to hydroxylated BP metabolites that were more soluble in aqueous media. (41 refs.)

77-5566 A Comparison of Benzo(a)pyrene Metabolism by Liver and Lung Microsomal Enzymes from 3-Methylcholanthrene-treated Rhesus Monkeys and Rats. (Eng.) Hundley, S. G. (Battelle Columbus Labs., Columbus, OH 43201); Freudenthal, R. I. *Cancer Res* 37(9): 3120-3125; 1977.

The effect of 3-methylcholanthrene (3-MC) on benzo(a)pyrene (BP) metabolism by the liver and lung of 3-MC-treated Rhesus monkeys and rats was determined. Differences in metabolite profiles and species or tissue sensitivity to aromatic hydrocarbon-induced carcinogenesis were studied. Metabolites formed by both tissues from two species were separated by high-pressure liquid chromatography and quantitated by liquid scintillation spectrometry. The metabolite profiles from untreated monkey and rat lung and from untreated monkey and rat liver were similar. However, treatment with 3-MC resulted in differing responses with regard to individual BP metabolite fractions. An unknown appeared that eluted between the 9,10- and 4,5-dihydrodihydroxy-BP (diol) fractions. The 9,10- and 7,8-diol fractions formed by

rat liver and monkey lung were increased to a greater degree than the other metabolite fractions. In the rat lung the BP, 1,6-dione fraction increased > 60 times and the 9-hydroxy-BP fraction increased > 50 times. The most pronounced increases in relative metabolite ratios resulting from 3-MC were in the 9,10- and 7,8-diol fractions from monkey lung and rat liver microsomal assays. In contrast, the 4,5-diol ratios from rat liver and monkey lung decreased substantially. (20 refs.)

77-5567 Synthesis of Perdeuteriobenzo(a)pyrene. (Ger.) Seibles, J. C. (Dept. Chemistry, Univ. Cincinnati, Cincinnati, OH 45221); Bollinger, D. M.; Orchin, M. *Angew Chem* 89(9): 667-668; 1977.

Perdeuteriobenzo(a)pyrene was synthesized by an exchange reaction with D₆ benzene at 110 C for 6 hr in the presence of the catalyst AlBr₃. The product contained 94.7 atom % deuterium. Deuterated benzo(a)anthracene, pyrene, chrysene, perylene, fluoranthene, carbazol, and triphenylene were prepared by the same method. Their photophysical properties are altered because of replacement of a hydrogen atom by a deuterium atom. The carcinogenic effect of perdeuterio-7,12-dimethylbenzo(a)anthracene was found to be twice as great as that of the nondeuterated compound. (8 refs.)

77-5568 Structures of Benzo[a]pyrene-Nucleic Acid Adducts Formed in Human and Bovine Bronchial Explants. (Eng.) Jeffrey, A. M. (Inst. Cancer Res., Columbia Univ., New York, NY 10032); Weinstein, I. B.; Jennette, K. W.; Grzeskowiak, K.; Nakanishi, K.; Harvey, R. G.; Autrup, H.; Harris, C. *Nature* 269(5626): 348-350; 1977.

Studies on RNA and DNA adducts of benzo[a]pyrene (BP) formed by human bronchial explants suggested that the structures of the major adducts were similar to those formed in the analogous bovine system. These data may contribute to the understanding of possible human hazards associated with environmental exposure to BP and other polycyclic hydrocarbons. (22 refs.)

77-5569 Comparative Metabolism of Benzo(a)pyrene and Drugs in Human Liver. (Eng) Kapitulnik, J. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Incorporated, Nutley, NJ 07110); Poppers, P. J.; Conney, A. H. *Clin Pharmacol Ther* 21(2): 166-176; 1977.

The oxidative metabolism of antipyrine, hexobarbital, coumarin, zoxazolamine, 7-ethoxycoumarin, and benzo(a)pyrene (BP) was studied in 32 adult human livers obtained

autopsy. BP hydroxylase activity was plotted separately against each of the other five enzymatic activities in each of the 32 livers, and highly significant statistical correlations were found between the hydroxylation of BP and that of antipyrine, hexobarbital, zoxazolamine, and coumarin. A correlation with borderline statistical significance was found between the hydroxylation of BP and the O-dealkylation of 7-hydroxycoumarin. The closest relationship found was that between the hydroxylations of BP and antipyrine. These results suggest the presence in human liver of multiple monooxygenase enzyme systems for the metabolism of BP and the five other substrates studied, as well as heterogeneity in their distribution among the 32 livers examined. (50 refs.)

77-5570 **Metabolism of Benzo[a]pyrene and 7,12-Dimethylbenz[a]anthracene in Cultured Human Bronchus and Pancreatic Duct.** (Eng) Harris, C. C. (Human Tissue Studies Section, Experimental Pathology Branch, Carcinogenesis Program, Building 37, Room 3A07, NCI, NIH, Bethesda, MD 20014); Autrup, H.; Stoner, G.; Yang, S. K.; Putz, J. C.; Gelboin, H. V.; Selkirk, J. K.; Connor, R. J.; Barrett, L. A.; Jones, R. T.; McDowell, E.; Trump, B. F. *Cancer Res* 37(9): 3349-3355; 1977.

The in vitro metabolism of two carcinogenic polynuclear aromatic hydrocarbons, benzo(a)pyrene (BP) and 7,12-dimethylbenz(a)anthracene (DMBA) in explants of human pancreatic duct and bronchus was examined. In cultured human bronchial mucosa, aryl hydrocarbon hydroxylase activity was inducible by both benz(a)anthracene (BA) and BP. High-pressure liquid chromatography revealed that prior BA exposure altered the qualitative features of the BP metabolite profile in the bronchial explants. The metabolite profiles of BP produced by normal-appearing bronchi from lung cancer patients were also compared with those from patients without lung cancer. The profiles were similar except for the higher percentage of organic solvent-extractable metabolites formed by bronchi from the noncancer patients that eluted from the column as a single peak. This peak cochromatographed with both the 9,10-diol and a triol of BP. DMBA was bound to the DNA of cultured human bronchial cells at higher levels than was BP. Binding of DMBA to DNA in human pancreatic duct was consistently less than that in cultured bronchi in the five patients studied. It was concluded that the human pancreatic duct and bronchus can activate polynuclear aromatic hydrocarbons into metabolic intermediates that bind to DNA and then into ultimate carcinogens. (36 refs.)

77-5571 **Experimental Production of Lingual Leukoplakia and Carcinoma.** (Eng) Marefat, P. (Dept. Oral Medicine, Harvard Sch. Dental Medicine, Boston, MA); Chhklar, G. *Oral Surg* 44(4): 578-586; 1977.

The combination of 7,12-dimethylbenz(a)anthracene

(DMBA, 0.05%) in acetone and trauma produced carcinoma of the tongue in 13/15 Syrian hamsters by 12-13 wk. The carcinomas were preceded by leukoplakic lesions. DMBA in mineral oil, together with similar trauma, resulted in dysplasia only by 15-16 wk. In the absence of trauma, DMBA in acetone produced carcinoma (4/7 animals), but with a longer latent period. Trauma alone or followed by acetone application did not induce neoplasms, although hyperkeratosis and dysplasia developed. (24 refs.)

77-5572 **Increased Cell Proliferation with Persistence of Circadian Rhythms in Hamster Cheek Pouch Neoplasms.** (Eng) Izquierdo, J. N. (Laboratorio de Oncologia, Instituto de Investigaciones de la Altura, Apartado 5045, Lima, Peru). *Cell Tissue Kinet* 10(4): 313-322; 1977.

The circadian rhythms during mitosis and DNA synthesis in squamous cell neoplasms induced by 7,12-dimethylbenz(a)anthracene (DMBA) in the Syrian hamster cheek pouch were compared with those in the normal hamster cheek pouch epithelium. The basal-like cell population of the neoplasms exhibited circadian rhythm in mitotic and labeling indices; the mitotic curve was preceded by the curve for DNA synthesis by about 3 hr. The highest proliferative activity occurred during the day and the lowest, at night. The fluctuating fractions of mitotic and DNA-synthesizing cells were considerably higher in the neoplasms than in the normal cheek pouch epithelium. The percent labeled mitoses curve showed that DNA synthesis lasted approx 6 hr and that the G₂ phase lasted about 2.5 hr; the S phase was about 30% shorter in neoplasms than in normal cheek pouch epithelium. The shortening of S phase may be related to the slight shift to the right of the circadian DNA-synthesis circadian rhythm curve in neoplasms as compared with the labeling curve of normal epithelium. (33 refs.)

77-5573 **Lysosomal Enzymes in Rat Sarcomas Induced by 7,12-Dimethylbenz(a)anthracene and Rous Sarcoma Virus.** (Eng) Hultberg, B. (Dept. Clinical Chemistry, Univ. Hosp., S-221 85 Lund, Sweden); Mitelman, F. *Hereditas* 86(1): 103-106; 1977.

The lysosomal apparatus in normal rat fibroblast cultures and in 7,12-dimethylbenz(a)anthracene (DBA)- and Rous sarcoma virus (RSV)-induced sarcoma cell cultures was compared. Both DMBA- and RSV-induced sarcoma cells showed relative increase of lysosomal enzyme activity outside the cells in the medium compared with the activity within the cells. An early equilibrium of enzyme activity level was reached in the medium from RSV sarcoma cells, but this was not seen in cultures of normal fibroblasts and DMBA sarcoma cells. There was a difference in intracellular content of lysosomal enzymes between RSV and DMBA sarcoma cells.

This was most evident for N-acetyl- β -glucosaminidase. These findings and the possible role of lysosomal enzymes in malignant cells are discussed. (17 refs.)

- 77-5574 **Effect of 7,12-Dimethylbenz(a)anthracene on the Binding of Aminoacyl Transfer RNA in Rat Liver.** (Eng) Chan, Y. P. (Dept. Medicine, Sunnybrook Medical Center, Univ. Toronto, Toronto, Ontario, Canada); Sendecki, W.; Nicholls, D. M. *Cancer Res* 37(11): 4220-4227; 1977.

Homogenates of the liver of female Sprague-Dawley rats obtained 2 or 7 days or 3 mo after iv injection of 7,12-dimethylbenz(a)anthracene (DMBA, 2.0 mg/rat/day for 3 days) were used to prepare ribosomes and postmicrosomal supernatant fractions and 0.5 M KCl salt wash fractions of the 40S ribosomal subunits. Amino acid incorporation by ribosomes was unchanged by DMBA. In peptide synthesis, the activity of the supernatant preparation, which contained limiting amounts of Elongation Factor 1 relative to Elongation Factor 2, was significantly increased at 2 days, but not 7 days, post-injection. This increase was due to the increased binding of phenylalanyl transfer RNA (tRNA). The factor-dependent binding of methionyl tRNA-fMet to control rat liver ribosomes was also markedly increased 2 days, but not 7 days, after injection. The livers of animals bearing mammary tumors 3 mo after DBMA injection also showed an increase in the binding of both aminoacyl tRNA species. (51 refs.)

- 77-5575 **Introduction of the BN Myelocytic Leukemia.** (Eng) Hagenbeek, A. (Radiobiological Inst. TNO, 151 Lange Kleiweg, Rijswijk ZH, Netherlands). *Leuk Res* 1(2/3): 85-90; 1977.

The cytology, cytochemistry, DNA content, and cytogenetics of the transplantable Brown Norway myelocytic leukemia (BNML), induced in a female rat of the inbred Brown Norway (BN) strain by 9,10-dimethyl-1,2-benzanthracene (3 injections of 2 mg), are described briefly. After many transplant generations in BN male rats, the karyotype of the BNML cells was found to be XY. This is suggestive of an infective agent in the original female (XX) cells, which might have been responsible for transformation of the male host cells. BN leukemia was classified as a slowly growing promyelocytic leukemia and considered to be a relevant model for human acute myelocytic leukemia. (2 refs.)

- 77-5576 **Development and Use of Model Systems of Mammary Cancer (Meeting Abstract).** (Eng.) Janss, D. H. (Endocrine Carcinogenesis Section, NCI-

Frederick Cancer Res. Center, Frederick, MD); Malan, L. B.; Hadaway, E. I.; DeAngelo, A. B.; Kelley, S. P. *J Toxicol Environ Health* 3(1/2): 359-360; 1977. (no refs.)

- 77-5577 **Comparative Effects of a Series of Prolactin Inhibitors, 17 β -Estradiol and 2 α -Methyldihydrotestosterone Propionate, on Growth of 7,12-Dimethylbenz(a)anthracene-induced Rat Mammary Carcinomas.** (Eng) Teller, M. N. (Donald S. Walker Lab., Sloan-Kettering Inst. Cancer Res., 145 Boston Post Road, Rye, NY 10580); Stock, C. C.; Hellman, L.; Mountain, I. M.; Bowie, M.; Rosenberg, B. J.; Boyar, R. M.; Budinger, J. M. *Cancer Res* 37(11): 3932-3938; 1977.

Eight ergot alkaloids and ergoline derivatives, effective prolactin inhibitors, were tested for activity against 7,12-dimethylbenz(a)anthracene-induced Sprague-Dawley rat mammary carcinomas. The compounds were administered daily, five times per week for 4 wk, and rats were observed for an additional 4 wk. Groups treated with androgen and estrogen were used as positive controls. The ergot compounds and ergolines that were highly effective in reducing tumor size or in inducing regression of tumors to nonpalpability were Deprenon (D-6-methyl-8-ergolin-1-ylacetic acid amide) and ergocryptine. Dironyl [N-(D-6-methyl-8-isoergolin-1-yl)-N',N'-diethylurea], ergocornine and Lysenyl [N-(D-6-methyl-8-isoergolenyl)-N',N'-diethylurea] were effective to an intermediate degree. Lergotril (2-chloro-6-methylergoline-8 β -acetonitrile), CB-154, and 6605-VUFB (D-6-methyl-8-cyanomethylergolin) were minimally effective. The remission of many individual carcinomas was brief, and the duration of complete regression (all tumors were nonpalpable) was < 10 wk. (51 refs.)

- 77-5578 **Prolactin Binding to 7,12-Dimethylbenz(a)anthracene-induced Mammary Tumors and Liver in Diabetic Rats.** (Eng) Smith, R. D. (Dept. Biochemistry, Univ. Rochester Medical Center, Rochester, NY 14642); Hilf, R.; Senior, A. E. *Cancer Res* 37(11): 4070-4074; 1977.

The growth of 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors and the specific¹²⁵I-labeled prolactin binding to membrane fractions prepared from livers and tumors were studied in Sprague-Dawley rats made diabetic by streptozotocin injection. Growth was inhibited in most tumors, and prolactin binding was reduced in both tumors and livers from diabetic animals. Prolactin binding to individual tumors varied widely in both intact and diabetic animals. Scatchard analysis of the binding data revealed that the apparent affinity of prolactin binding to liver and tumor membranes was similar (K_a approx $3.0 \times 10^9 M^{-1}$) and was not affected by diabetes. The reduction in prolactin binding

o tumors may render these tissues less responsive to prolactin, thus explaining, at least in part, the observed inhibition of tumor growth in diabetic rats. However, some tumors in diabetic animals regressed despite relatively high levels of prolactin binding. Therefore, additional factors must play important roles in the mechanisms(s) by which the growth of DMBA-induced tumors is impaired in the diabetic rat. (28 refs.)

77-5579 **Effects of Azathioprine and *Corynebacterium parvum* on Dimethylbenzanthracene-induced Mammary Tumors in Rats.** (Spa) Rifa, J. (Laboratorio Experimental de Investigacion del Cancer, Servicio de Oncologia y Medicina Nuclear, Hosp. de la Santa Cruz y San Pablo, Barcelona, Spain); Figueras, A.; Angel Navarro, M.; Bordes, R.; Viladiu, P. *Rev Esp Oncol* 23(2): 225-232; 1977.

The effect of azathioprine (ATP) or *Corynebacterium parvum* (C.p.) on the induction of rat mammary tumors by dimethylbenzanthracene (DMBA) was studied in female rats administered a single dose of 20 mg of DMBA in 1 ml of sesame oil by gastric intubation on day 0. C.p., 0.5 mg in 1 ml of phosphate-buffered saline, was administered ip to one group of rats every 10 days from day 45 to day 105, the end of the experiment. Another group received ATP (0.05 mg in 1 ml of sesame oil) twice a week by gastric intubation starting on day 30, and a third group received ATP starting on day 45. Control groups received either sesame oil or no treatment after ingestion of DMBA. The av time for the appearance of the first tumor after DMBA ranged from 73 to 86 days. All the tumors were adenocarcinomas. C.p. did not have any effect on tumor development and growth. In the group administered ATP on day 30, only 30% of the rats had tumors compared to 70%-80% for controls. When ATP was administered on day 45, the percentage of animals with tumors did not differ from the control groups, but there was an increase in the number of tumors per animal (4.7 tumors/animal compared with 2-2.3 tumors/animal in controls). It is concluded that the effects of ATP on the induction and promotion of DMBA-induced tumors during the first 30 days of carcinogenesis may be due to its cytotoxic potency and that its immunosuppressant effect becomes manifest only after 45 days, when the tumor cell population is sufficiently large. (17 refs.)

77-5580 **The Metabolic Activation of 7-Methylbenz(a)anthracene: The Induction of Malignant Transformation and Mutation in Mammalian Cells By Non-K-Region Dihydrodiols.** (Eng.) Marquardt, H. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Baker, S.; Tierney, B.; Grover, P. L.; Sims, P. *Int J Cancer* 19(6): 828-833; 1977.

A study was made of the ability of 7-methylbenz(a)anthracene (MBA) and four MBA-

dihydrodiol derivatives to transform mouse M2 fibroblasts and cause mutations in V79 Chinese hamster cells. The K-region dihydrodiol (MBA-5,6-diol) was inactive in bringing about transformation; the transforming ability of the other dihydrodiols declined in the order MBA-3,4-diol > MBA-8,9-diol > MBA > MBA-1,2-diol. A similar order of activity was seen when mutagenicity was determined. The data support the general hypothesis that non-K-region dihydrodiols, which can be metabolized to vicinal diol epoxides, are important in the metabolic activation of polycyclic hydrocarbons and that 3,4-dihydro-3,4-dihydroxy-7-MBA is most probably involved in the metabolic activation of MBA. (31 refs.)

77-5581 **Excision Repair of DNA in 7-Bromomethylbenz(a)anthracene-treated Chinese Hamster and HeLa Cells.** (Eng) Dipple, A. (Frederick Cancer Res. Center, P. O. Box B, Frederick, MD 21701); Roberts, J. J. *Stud Biophys* 61: 23-28; 1977.

Excision repair in HeLa S-3 and V79 379A Chinese hamster cells was investigated following exposure of the cells to 7-bromomethylbenz(a)anthracene (BMBA) at various concentrations. Following exposure to 2 μ M BMBA, the hamster cells synthesized more DNA than the HeLa cells. There was extensive excision of adducts formed after exposure for 3-30 hr, ranging from 10%-25% in HeLa cells exposed to 0.6 μ M to 15%-37% in cells exposed to 0.2 μ M. The corresponding figures in the V79 cells were 1%-4% in cells exposed to 1.8 μ M, 17%-47% in cells exposed to 0.2 μ M, 16%-52% in cells exposed to 0.1 μ M. The specificity of the excision was evident in the finding that the half-life for removal of modified guanine residues was approx twice that for removal of modified adenine residues. There was no indication of a selective effect of high concentrations of carcinogen on excision of either base. It is believed that these findings are relative to polycyclic hydrocarbon carcinogens in general. (15 refs.)

77-5582 **Inhibition by Caffeine of Post-replication Repair in Chinese Hamster Cells Treated with 7-Bromomethylbenz(a)anthracene: Enhancement of Toxicity, Chromosome Damage and Inhibition of Ligation of Newly-synthesized DNA.** (Eng.) Roberts, J. J. (Inst. Cancer Res., Chemical Carcinogenesis Div., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks, HP8 4SP, England); Friedlos, F.; Van den Berg, H. W.; Kirkland, D. *J. Chem Biol Interact* 17(3): 265-290; 1977.

The effect of caffeine on V79-379A Chinese hamster cells after treatment with 7-bromomethylbenz(a)anthracene (BMBA) was investigated. Exponentially-growing cells were treated with 0-0.4 μ M of BMBA in acetone for 30 min, with 0.75 mM caffeine. Posttreatment incubation in caffeine

dramatically enhanced the cytotoxic action of BMBA; furthermore, by 24 hr, there was a dramatic increase in the number of cells showing chromosomal aberrations. Caffeine partially reversed the dose-dependent depression in DNA synthesis induced by BMBA. Newly synthesized DNA (low mol wt) in the caffeine-treated cells resulted from an inhibition of DNA ligation. The size of the nascent DNA approximated the distance between arylalkylations on the template strand of DNA. It is suggested that caffeine leads to the formation of gaps in the newly-synthesized DNA opposite almost all DNA adducts and that a caffeine-sensitive repair process may be a characteristic response of cells to carcinogenic agents. Caffeine may thus be a valuable tool in the detection of carcinogenic compounds. (62 refs.)

- 77-5583 **Chemical Transformation of Rat Cells Infected with Xenotropic Type-C RNA Virus and Its Suppression by Virus-specific Antiserum.** (Eng.) Price, P. J. (Microbiological Associates, Torrey Pines Res. Center, La Jolla, CA 92037) Suk, W. A.; Peters, R. L.; Gilden, R. V.; Heubner, R. J. *Proc Natl Acad Sci USA* 74(2): 579-581; 1977.

Fischer rat embryo cells infected with xenotropic mouse type-C RNA viruses isolated from NIH Swiss mice or C57L inbred mice were transformed by 0.1 μ g of either 4-nitroquinoline oxide or 3-methylcholanthrene under conditions in which neither treatment alone induced transformation. Transformation depended on the presence of actively growing virus at the time of treatment. Specific antibody to xenotropic virus neutralized the virus and inhibited malignant transformation by 3-methylcholanthrene. (14 refs.)

- 77-5584 **The Metabolism and DNA Binding of 3-Methylcholanthrene.** (Eng.) King, H. W. (Chemical Carcinogenesis Div., Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks. HP8 4SP, England); Osborne, M. R.; Brookes, P. *Int J Cancer* 20(4): 564-571; 1977.

Tritiated 3-methylcholanthrene (3-MC) was administered to cultured mouse embryo cells from which DNA was later isolated and hydrolyzed to deoxyribonucleosides. The hydrolysate was analyzed by LH20 chromatography, high-pressure liquid chromatography, and fluorescence spectroscopy. The 3-MC-nucleoside products were compared with the nucleoside derivatives from 3-MC 11,12-oxides-treated DNA and found to differ in both fluorescence spectra and chromatographic behavior. Microsome-catalyzed DNA binding of primary metabolites of 3-MC identified two metabolites for which the DNA reaction was extensive. These metabolites were characterized by their chromatographic and spectrophotometric properties. The products of their microsome-induced DNA binding were isolated, and comparison with the products derived from a cell-mediated 3-MC-DNA reac-

tion suggested that these metabolites might be precursors of this latter reaction. The chemical nature of the metabolites and of their DNA reaction products is discussed in relation to the "bay region" and carbonium ion concepts of the ultimate carcinogen of polycyclic hydrocarbons. (31 refs.)

- 77-5585 **Sequential Ultrastructural Alterations in the Mouse Epidermis after a Single Subcutaneous Injection of 20-Methylcholanthrene.** (Eng) Bhisey, R. A. (Ultrastructure Div. Cancer Res. Inst. Parel, Bombay-400 012, India); Sirsat, S. M. *Indian J Cancer* 14(1): 18-24; 1977.

Sequential fine-structural alterations in Swiss albino mice epidermis were studied after a single sc injection of 20-methylcholanthrene (20-MC, 0.5 mg) dissolved in thiophene-free benzene. Within 24 hr of administration, 20-MC caused epidermal destruction that was reversed by 1 wk. Between 2 and 6 wk, 20-MC induced cellular evolution, resulting in development of altered cell foci. The altered cells contained few tonofibrils, and showed mutual detachment, dissociation from the basal lamina, and inability to form desmosomes. Intercellular spaces were wide and open. These cells developed slender cytoplasmic processes by means of which they occasionally invaded the dermis. It is proposed that these altered cells represent transformed latent tumor cells susceptible to a further promoting stimulus. (20 refs.)

- 77-5586 **Influence of a Chronic Environmental Stress on the Incidence of Methylcholanthrene-induced Tumors.** (Eng) Baker, D. G. (Claire Zellerbach Saroni Tumor Inst., Mount Zion Hosp. and Medical Center, San Francisco, CA 94115). *Cancer Res* 37(11): 3939-3944; 1977.

The influence of a chronic environmental stress, ie, living in a 2 C environment, on the incidence of methylcholanthrene (MC)-induced tumors in albino female Simonsen rats, a Sprague-Dawley-derived strain, was studied. The metabolic rate was double for rats kept at 2 C compared with those kept at 25 C. Exposure to 2 C for life, with no other treatment, reduced median life expectancy to 560 days compared with 686 days for rats kept at 25 C. Transfer to a 2 C environment after 250 days at 25 C reduced the incidence of spontaneous tumors, but transfer to 25 C after 250 days at 2 C increased the incidence compared with that for rats always kept at 25 C. Exposure to 2 C immediately following MC administration (2 mg sc) significantly reduced tumor incidence compared with that in rats kept at 25 C but did not change tumor induction time. The reduced tumor incidence may have resulted from inhibition of carcinogenic transformation by chronic stress. The survival time of rats with MC-induced tumors was not significantly less in 2 C environment than it was at 25 C. (28 refs.)

- 77-5587 **Patterns of Growth and Ribosome Accumulation during 3-Methylcholanthrene-induced Epidermal Hyperplasia.** (Eng) Mueller, S. N. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA 19104); Argyris, T. S. *Cancer Res* 37(9): 3400-3405; 1977.

The pattern of ribosomal (r)RNA accumulation in albino CD-1 female mice treated with a single topical application of either 1, 2, or 4 μ moles of 3-methylcholanthrene (3-MC) was determined. 3-MC was applied to the backs of the mice 2 days after hair had been removed. One day after treatment, the number of suprabasal cell nuclei/mm interfollicular epidermis increased for all doses, but extensive cell injury was not apparent until day 3. There was a 15% decrease in basal cells for 2 days after 1 μ mole, a 24 to 45% decrease for 3 days after 2 μ moles, and a 19 to 54% decrease for 4 days after 4 μ moles. By day 21, the epidermis had almost returned to normal. There was no significant rRNA accumulation (indicated by total rRNA per cm^2 epidermis) until day 2 for the lower doses and day 4 for the higher one. The rRNA accumulation was 5.5 times normal at day 5 for the lowest dose and 9 times normal at day 7 for the higher doses. This increase was characterized by an initial peak before cell injury was apparent, a decrease, and another increase by day 4 or 5. By day 14, when the epidermis was still hyperplastic, the rRNA was still increased to about twice normal; by day 21, cellular ribosomal levels were normal. There appeared to be proportionate increases in free and membrane-bound rRNA. Cellular growth regulation and rRNA accumulation are integrated. (23 refs.)

- 77-5588 **Factors Influencing the Measurement and the Reproducibility of Aryl Hydrocarbon Hydroxylase Activity in Cultured Human Lymphocytes.** (Eng.) Gurtoo, H. L. (Dept. Experimental Therapeutics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263); Minowada, J.; Paigen, B.; Parker, N. B.; Hayner, N. T. *J Natl Cancer Inst* 59(3): 787-798; 1977.

Factors affecting the measurement and reproducibility of aryl hydrocarbon hydroxylase (AHH) activity in cultured human lymphocytes were studied. Optimal AHH activity occurred after 72 hr, and the AHH inducibility ratio was affected by the starting cell density. Storing whole blood for 24 hr reduced AHH activity, but storing purified lymphocytes in RPMI-1640 at room temperature minimized AHH loss. DNA determinations performed after enzyme assay were more reliable than cell counts in determining specific AHH activity. When phytohemagglutinin (PHA) and concanavalin A were used as mitogens, AHH activity correlated well with cellular DNA content and with blastogenesis. This was not the case, however, when pokeweed mitogen (PWM) or lipopolysaccharides were used. Different lots of fetal calf serum also significantly affected AHH activity. When conditions were strictly controlled, when lymphocytes were cultured in mixed-mitogen combinations (1:100 dilution each of

PHA and PWM), and when 3-methylcholanthrene was used as the inducer, the AHH inducibility ratio in repeat determinations on the same individual was much less variable than either the corresponding basal and induced AHH activities or the degree of blastogenesis. (28 refs.)

- 77-5589 **Aryl Hydrocarbon Hydroxylase Inducibility and Carcinoma of Renal Pelvis and Ureter (Letter to Editor).** (Eng.) Trell, E. (Section Preventive Medicine, Univ. Lund, Malmo General Hosp., Malmo, Sweden); Oldbring, J.; Korsgaard, R.; Mattiasson, I. *Lancet* 2(8038): 612; 1977.

Thirty patients with cancer of the renal pelvis and ureter were studied to determine the correlation between smoke-induced aryl hydrocarbon hydroxylase and this cancer. The data did not indicate that this enzyme is a major carcinogen activator in these tumors. (11 refs.)

- 77-5590 **Comparison Between Aryl Hydrocarbon Hydroxylase (AHH) Activity in Human Lung Tissue, Pulmonary Macrophages (PAMs), and Blood Lymphocytes (L) (Meeting Abstract).** (Eng.) Martin, R. R. (Dept. Medicine, Baylor Coll. Medicine, Houston, TX); McLemore, T. L.; Pickard, L. R.; Wray, N. P.; Mattox, K. L.; Guinn, G. A. *Clin Res* 25(4): 626A; 1977. (no refs.)

- 77-5591 **Comparison of Aryl Hydrocarbon Hydroxylase Induction in Cultured Blood Lymphocytes and Pulmonary Macrophages.** (Eng) McLemore, T. L. (Dept. Medicine, Baylor Coll. Medicine, Houston, TX 77030); Martin, R. R.; Toppell, K. L.; Busbee, D. L.; Cantrell, E. T. *J Clin Invest* 60(5): 1017-1024; 1977.

Aryl hydrocarbon hydroxylase (AHH) induction was studied in cultured peripheral blood lymphocytes and pulmonary alveolar macrophages from 15 smokers and 8 nonsmokers with pulmonary diseases. Enzyme levels in lymphocytes from cigarette smokers cultured in medium without an inducing agent were 57 milliunits (mU)/ 10^6 cells compared with 20 mU/ 10^6 cells in lymphocytes from nonsmokers. When lymphocytes were cultured in the presence of the inducing agents benzo(a)anthracene (BA), enzyme activity increased to 168 mU/ 10^6 cells from smokers and 99 mU/ 10^6 cells from nonsmokers. Noninduced enzyme values in cultured macrophages were 45 mU/ 10^6 cells for smokers vs 24 mU/ 10^6 cells for nonsmokers. However, in the presence of BA, pulmonary macrophages from smokers or nonsmokers had similar levels of induced enzyme activity ($p > 0.1$). A positive correlation was observed

for nonsmokers or smokers when enzyme values for noninduced cultures of macrophages and lymphocytes from individual patients were compared simultaneously. Enzyme values for macrophages and lymphocytes cultured in the presence of an inducer also revealed a positive correlation for individual smokers or nonsmokers. Inducibility (expressed as fold-induction) for macrophages and lymphocytes from individual patients was also positively correlated. These results indicate that the capacity for AHH induction is similar whether tested in lymphocytes or pulmonary macrophages of pulmonary disease patients. (30 refs.)

- 77-5592 **Genetics of Aryl Hydrocarbon Hydroxylase Induction in Mice: Response of the Lung to Cigarette Smoke and 3-Methylcholanthrene.** (Eng) Abramson, R. K. (Medical Services, Veterans Admin. Hosp., Lexington, KY 40507); Taylor, B. A.; Tomlin, D.; Hutton, J. J. *Biochem Genet* 15(7/8): 723-740; 1977.

Mouse strains AKR/J (aromatic hydrocarbon nonresponsive) and C57BL/J (aromatic hydrocarbon responsive) and six recombinant inbred (RI) lines derived from them were tested for aryl hydrocarbon hydroxylase (AHH) response in lung and liver to parental 3-methylcholanthrene (3-MC: 100 mg/kg ip) or cigarette smoke inhalation, to determine if induction of AHH in liver and lung is regulated by the same genes. Inducibility (ratio of 3-MC-induced AHH activities to basal AHH activities) in the liver of 3-MC-treated RI mice was bimodal and compatible with a Mendelian segregation of genes at a small number of loci, probably one or two. Increased AHH activities in 3-MC-treated liver were associated with increased ability to metabolize benzo(a)pyrene and whole smoke condensates to mutagens detected by *Salmonella typhimurium* TA1538. AHH inducibility in lung in response to 3-MC was not bimodal. There was a correlation between AHH levels in liver and lung when actual levels of AHH activity were measured following the administration of 3-MC, which suggests that some genes affecting liver also affect lung. Basal and 3-MC-induced AHH levels in lung were also correlated. AHH induction in pulmonary tissues occurred in all mice after either parenteral 3-MC or smoke inhalation. AHH activities in lung following smoke inhalation were not correlated with AHH levels in liver after 3-MC and were only weakly correlated with basal pulmonary levels. The correlation between 3-MC-induced and smoke-induced AHH activities in lung was weak. It is concluded that the genetic regulation of AHH activity in lung is not as simple as the genetic regulation of AHH activity in liver and that the genetic regulation of AHH activity in mouse lung (rather than mouse liver) most closely parallels the pattern of AHH induction in human lymphocytes. (34 refs.)

- 77-5593 **Characterization of Lipid Inclusions in Alveolar Macrophages after Tobacco Smoke Exposure**

(Meeting Abstract). (Eng.) Davies, P. (Boston, MA); Engel, E.; Huber, G. *Chest* 72(3): 397; 1977. (no refs.)

- 77-5594 **Changes in the Composition of Rat Lungs after Exposure to Cigarette Smoke.** (Eng) Stewart, P. S. (Group Res. and Development Centre, British-American Tobacco Co. Limited, Southampton, Hants, England). *Proc Eur Soc Toxicol* 18: 218-221; 1977.

Changes in female Wistar rat lungs were investigated after they were exposed to cigarette smoke:air ratios of 1:8 and 1:12 from 12 cigarettes. After a 5-day smoke acclimatization period, the rats were subjected to two 9-min exposures per day for up to 14 days. Exposed animals had a reduced wt gain, although there was no variation in lung wt between exposed and control animals. Exposure at both levels increased acid phosphatase activity up to a max at 7 days. This activity decreased following continued exposure, and it eventually returned to normal. β -Glucuronidase levels increased in exposed animals, but they returned to normal after cessation of exposure. Elastin levels increased to a max at 14 days; they remained high for several days and returned to normal by the end of the experiment. Collagen levels also increased. The increase was much more rapid after exposure to the 1:12 dilution, but all levels returned to normal after cessation of exposure. Hexosamine content increased rapidly and then returned to normal within 7-12 days; this timing suggests a dose-related sensitivity. The hexosamine response could provide a basis for comparing smoke irritancy. (5 refs.)

- 77-5595 **Alterations in Lung Parenchyma Following Experimental Chronic Inhalation of Tobacco Smoke (Meeting Abstract).** (Eng.) Nicholas, H. (Boston, MA); Davies, P.; Sornberger, C.; Huber, G. *Chest* 72(3): 409; 1977. (no refs.)

- 77-5596 **Simulation of Smoking Conditions by Pyrolysis.** (Eng) Higman, E. B. (Tobacco Lab., Agricultural Res. Service, U.S. Dept. Agriculture, Athens, GA 30604); Severson, R. F.; Arrendale, R. F.; Chortyk, O. T. *J Agric Food Chem* 25(5): 1201-1207; 1977.

A method of controlled pyrolysis is described that simulates cigarette smoking closely and produces pyrolyzate fractions with a polynuclear aromatic hydrocarbon (PAH) profile nearly identical to that of cigarette smoke. This method was developed for evaluation of the potential of different tobacco varieties to produce possibly hazardous smoke compounds. Puff time, temperature, oven rate, and nitrogen flow were varied to produce fraction yields of PAH, neutrals, bases, acids, and phenols that were the same as those of cigarette

smoke. Gas chromatographic analyses of the pyrolyzate and cigarette smoke condensate fractions showed quantitative agreement between their PAH profiles. (11 refs.)

77-5597 Determination of the Carcinogenic Activity of Some Chemical Substances by a Rapid Test Method. (Rus.) Garibian, D. Kh. (Inst. Roentgenology and Oncology, Ministry Public Health Armenian SSR, Erevan, USSR); Papoian, S. A. *Gig Sanit* (8): 74-76; 1977.

The possible carcinogenic effects of tobacco smoke tar, sodium dichromate, chloroprene, and vinyl acetate were studied in 870 random-bred mice aged 2-3 mo. The substances were applied to the skin in single doses or three times per week in a 30-day experiment. The carcinogenic effects were evaluated by a rapid method based on the disappearance of the sebaceous glands. Cigarette tar caused the sebaceous glands to disappear after 5-11 days, but the glands reappeared after 15 days. Thickening of the skin, crust formation, progressive hyperplasia, and dystrophy of the epidermis were seen. Sodium dichromate, chloroprene, and vinyl acetate did not cause the sebaceous glands to disappear. The findings, in keeping with the results of other studies, suggest that cigarette tar is carcinogenic but that the other substances tested are not. (3 refs.)

77-5598 More Hydatidiform Moles? (Letter to Editor) (Eng.) Calvert, J. P. (Ipswich Hosp., Heath Road Wing, Ipswich, Suffolk, England). *Br Med J* 2(6086): 578-579; 1977.

The question is raised as to whether an increased incidence in hydatidiform moles seen at one hospital following a severe drought may be a direct result of an increase in nitrate concentration in the drinking water of the area. (4 refs.)

77-5599 Ascorbic Acid Prevents Liver Tumour Production by Aminopyrine and Nitrite in the Rat. (Eng.) Chan, W. C. (Dept. Pathology, Univ. Hong Kong, Hong Kong); Fong, Y. Y. *Int J Cancer* 20(2): 268-270; 1977.

The protective effect of ascorbic acid on liver tumor production by aminopyrine and nitrite was investigated in male Sprague-Dawley rats. Group A (40 rats) were fed laboratory chow and received aminopyrine (1 g/liter) and sodium nitrite (1 g/liter) in the drinking water. Group B (40 rats) was similarly treated, but the diet was supplemented with 7 g/kg vitamin C. There were 40 control rats in Group C. It was estimated that each rat consumed approx 39 g over the 40 wk experiment. In Group A 31/37 rats examined had one or more tumors in the lung (25), liver (12), or kidney (10). In

group B, tumors were present in 14/39 rats examined; these occurred in the lungs (13) and kidneys (7). There were no tumors in group C. Most tumors were adenocarcinomas of the lung. Liver tumors in group A were hepatocellular carcinomas, except for one spindle-cell fibrosarcoma and one hemangioendothelioma. Cystic changes were found in the biliary ducts of 18 rats in group A (4 of these also had tumors) and 6 rats in group B. Most of the kidney tumors were adenomas of tubular origin. Three rats in group A had bilateral tumors: in one, the tumor was a spindle cell sarcoma; in one, an anaplastic round cell tumor; and in the third, both sarcomatous and adenomatous components were present. These findings demonstrate the protective effect of vitamin C on tumor formation; this protection is due in part to blockade of in vivo nitrosation. (9 refs.)

77-5600 Transplacental Chronic Toxicity Test of Carbaryl with Nitrite in Rats. (Eng.) Lijinsky, W. (Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD 21701); Taylor, H. W. *Food Cosmet Toxicol* 15(3): 229-232; 1977.

Pregnant female Sprague-Dawley rats were given a total of 300 mg carbaryl by gavage over a 10-day period. This dose of carbaryl had no apparent life-shortening effect on either the treated animals or their offspring. The tumors that occurred (mammary fibroadenomas, pituitary tumors, adrenal tumors, some islet-cell tumors of the pancreas, and a few hepatocellular carcinomas) were those normally found in Sprague-Dawley rats. The distribution of these tumors did not suggest any drug-related effect on their incidence. (9 refs.)

77-5601 On the Aetiology of Gastric Cancer: Mutagenicity of Food Extracts after Incubation with Nitrite. (Eng.) Marquardt, H. (Naylor Dana Inst. Disease Prevention, Valhalla, NY 10595); Rufino, F.; Weisburger, J. H. *Food Cosmet Toxicol* 15(2): 97-100; 1977.

Extracts of nitrite-treated foods were examined for their mutagenicity in a search for etiological factors in gastric carcinogenesis. Treating fish, beans, and borscht with sodium nitrite (1,000-20,000 ppm) resulted in the production of one or more temperature-sensitive (100 C) mutagenic factors, as indicated by tests with different strains of *Salmonella typhimurium*. Strain TA1535 was the most sensitive indicator organism tested, and mutagenesis was highest (297-311 his⁺ revertant colonies) at pH 3 and at 5,000-20,000 ppm nitrite. The use of more acidic or alkaline media reduced the observed mutagenicity over a 24-hr period. Incubation with ascorbic acid (28,000 ppm) completely prevented mutagenesis by nitrite-treated fish. Treating hot dogs, pork, beef, barley, and sour milk with nitrites produced no detectable mutagens. (17 refs.)

- 77-5602 Feeding Tests in Rats on Mixtures of Nitrite with Secondary and Tertiary Amines of Environmental Importance.** (Eng) Lijinsky, W. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN); Taylor, H. W. *Food Cosmet Toxicol* 15(4): 269-274; 1977.

Groups of 30 Sprague-Dawley rats (15 males 15 females) were given 60 ml of an amino compound solution to drink 5 days/wk, ad lib, for 50-90 wk. The following amines were tested: arginine (0.1% in water), chlordiazepoxide (0.2%), chlorpromazine (0.2%), cyclizine (0.1%), dimethyldodecylamine (0.18%), dimethylphenylurea (0.1%), hexamethylenetetramine (0.1%), lucanthone (0.14%), methapyriline (0.1%), methylguanidine (0.1%), piperidine (0.09%), tolazamide (0.1%), and trimethylamine oxide (0.08%). Sodium nitrite was added to the solutions in a dose range of 0 to 0.2%, and the possible in vivo formation of N-nitroso compounds from these ingested amines was examined. Only a small number of amines, either alone or with nitrite, induced a significant number of tumors. Lucanthone gave a 30% incidence of liver tumors when given alone, but not when given with nitrite. Nervous system tumors occurred in 10% of the animals receiving a combination of chlordiazepoxide and nitrite, hepatic tumors occurred in 30% receiving methapyriline plus nitrite, and 10% of the rats had urinary bladder tumors after administration of dodecylamine plus nitrite. However, ingestion of secondary and tertiary amines in combination with nitrite can result in the formation of significant quantities of carcinogenic N-nitroso compounds. (25 refs.)

- 77-5603 Metabolism of Acyclic and Cyclic N-Nitrosamines in Cultured Human Bronchi.** (Eng) Harris, C. C. (Human Tissue Studies Section, Experimental Pathology Branch, Carcinogenesis Program, Div. Cancer Cause and Prevention, NCI, Bethesda, MD 20014); Autrup, H.; Stoner, G. D.; McDowell, E. M.; Trump, B. F.; Schafer, P. *J Natl Cancer Inst* 59(5): 1401-1406; 1977.

The metabolism of four polynuclear aromatic hydrocarbons found in cigarette smoke, N-nitrosodimethylamine (DMN), N-nitrosodiethylamine (DEN), N-nitrosopyrrolidine (NPY) and N-nitrosopiperidine (NPd), and one, N,N'-dinitrosopiperazine (DNP), that is not, was investigated in cultured human bronchi from three lung cancer patients and one patient who died of a head injury. ¹⁴C was added, and the amount of labeled CO₂ given off was measured. Measurable CO₂ was formed by the cultures from DMN, DEN, and NPY in 4/4 patients, DNP 3/4 patients, and NPd in only 1/4 patients. The patient with the head injury lacked only NPd. Since CO₂ formation is only one of several metabolic pathways, it can be assumed that the metabolism of these compounds was greater than that observed. The labeled nitrosamines and/or their metabolites were bound to protein and to DNA, but the binding levels were usually severalfold higher with the protein. Binding levels of DNP were as high as those with DMN and DEN, but binding levels of NPY and NPd were lower. (35 refs.)

- 77-5604 Nonenzymatic Microbial Acceleration of Nitrosamine Formation.** (Eng) Yang, H. S. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA 02139); Okun, J. D.; Archer, M. C. *J Agric Food Chem* 25(5): 1181-1183; 1977.

Rates of formation of various dialkyl nitrosamines were accelerated at pH 3.5 in the presence of several gram-negative and gram-positive bacteria and of yeast. The magnitude of rate enhancements was similar for both heat-killed and untreated cells and depended on alkyl chain length. The effect therefore appears to be nonenzymatic. (16 refs.)

- 77-5605 Diallylnitrosamine: A Potent Respiratory Carcinogen in Syrian Golden Hamsters: Brief Communication.** (Eng) Althoff, J. (Eppler Inst. Res. in Cancer, 42nd St. and Dewey Ave., Omaha, NB 68105); Grandjean, C.; Gold, B. *J Natl Cancer Inst* 59(5): 1569-1571; 1977.

The carcinogenic effect of sc injections of diallylnitrosamine (DAN) on 8-wk-old Syrian golden hamsters was investigated. Animals were given a single injection of 500, 1,000, 2,000, or 4,000 mg/kg or weekly injections for life of 130, 65, or 32.5 mg/kg. The sc LD₅₀ was 1,416 mg/kg in females and 1,230 mg/kg in males. Of nine animals treated with 1,000 mg/kg, the average age at death was 53 wk, and five developed respiratory tract tumors. Of the three 30-hamster groups treated for life with 130, 65, or 32.5 mg/kg, the average age at death was 44, 47, and 48 wk, and respiratory tract tumors occurred in 29, 29, and 18 animals, respectively. The effect was dose-dependent. The nasal cavity, larynx, and trachea were the sites most affected and most of the tumors were adenocarcinomas and papillary polyps. (17 refs.)

- 77-5606 Further Studies on the Effect of Leupeptin, a Protease Inhibitor, on Induction of Bladder Tumors in Rats by N-Butyl-N-(4-hydroxybutyl)nitrosamine.** (Eng) Kakizoe, T. (Dept. Urology, Faculty Medicine, Univ. Tokyo, Bunkyo-ku, Tokyo 113, Japan); Esumi, H.; Kawachi, T.; Sugimura, T.; Takeuchi, T.; Umezawa, H. *J Natl Cancer Inst* 59(5): 1503-1508; 1977.

The effect of leupeptin on N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN)-induced bladder tumors in male W rats was investigated. Three groups of 20 rats received 0.01% BBN in their drinking water for 12 wk. A basal powder diet supplemented with 0.1% leupeptin was given to Group A throughout the experiment (40 wk), and to Group B when BBN administration was stopped. Group C was given the basal diet without leupeptin for the entire 40 wk. The average number of bladder tumors in the three groups was 3.2 for A, 4.0 for B, and 2.6 for C. The incidence of hyperplasia, papilloma, cancer, and invasion was 100%, 100%, 75.0% and 12.5% in Group A; 100%, 100%, 92.3%, and 46.2% in

Group B; and 100%, 93.8%, 62.5%, and 12.5% in Group C. No distant metastases were found. When leupeptin was administered during the promotion stage, it increased tumor size and the incidence of cancer and invasion. Administration of the compound for the entire experiment counteracted this effect. The mechanism of action for leupeptin is not known. (15 refs.)

- 77-5607 A Potent Pancreatic Carcinogen in Syrian Hamsters: *N*-Nitrosobis(2-oxopropyl)amine.** (Eng) Pour, P. (Eppley Inst. for Res. In Cancer, Univ. Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NB 68105); Althoff, J.; Kruger, F. W.; Mohr, U. *J Natl Cancer Inst* 58(5): 1449-1453; 1977.

N-Nitrosobis(2-oxopropyl)amine (BOP), a postulated further β -metabolite of di-*n*-propylnitrosamine, induced a high incidence of pancreatic duct carcinomas and adenocarcinomas in Syrian hamsters receiving weekly sc injections (doses of 2.5-10 mg/kg) for life. The tumors appeared as early as 13 wk. BOP also induced pancreatic adenomas, which appeared after 28 wk, in hamsters given a single sc dose (62.5-500 mg/kg). Compared with the related pancreatic carcinogens *N*-nitrosobis(2-hydroxypropyl)amine and *N*-nitrosobis(2-acetoxypropyl)amine, BOP induced only few neoplasms of the lung, liver, and kidney, and none in the nasal cavity, larynx, and trachea. These results are important for the development of a more specific model for pancreatic carcinogenesis studies. (13 refs.)

- 77-5608 Experimental Carcinoma of Liver in Macaque Monkeys Exposed to Diethylnitrosamine and Hepatitis B Virus.** (Eng) Gyorkey, F. (Dept. Pathology, Veterans Admin. Hosp., Houston, TX 77211); Melnick, J. L.; Mirkovic, G. A.; Cabral, G. A.; Gyorkey, P.; Hollinger, F. B. *J Natl Cancer Inst* 59(5): 1451-1467; 1977.

The effects of diethylnitrosamine (DENA; 20 mg/kg ip, bi-weekly for 2 yr) and hepatitis B virus (HBV; 1 or 2 2-ml injections iv) on macaque monkeys were investigated by virus serology and by light and electron microscopy. The experimental groups comprised 43 newborn or juvenile cynomolgus and rhesus monkeys of both sexes. HBV neither had a carcinogenic effect nor increased the oncogenicity of DENA. However, HBV given to juvenile primates before DENA treatment resulted in gross and microscopic alterations consistent with mild hepatitis and postnecrotic cirrhosis; multifocal liver carcinomas apparently developed within these cirrhotic nodules. The pathologic findings in the experimental animals were strikingly similar to those observed in liver cancer patients. (32 refs.)

- 77-5609 Further Studies on the Metabolism of Dimethylnitrosamine by Rat Liver In Vitro.** (Eng)

Lake, B. G. (British Industrial Biological Res. Assoc., Woodmansterne Road, Surrey SM5 4DS, England); Cottrell, R. C.; Phillips, J. C.; Gangolli, S. D.; Lloyd, A. G. *Biochem Soc Trans* 5(4): 1013-1015; 1977.

A study was conducted to test the hypothesis that hepatic dimethylnitrosamine degradation proceeds through an N-oxide intermediate catalyzed by a microsomal amine oxidase enzyme. Results indicate that this degradation is markedly affected by the monoamine oxidase substrate benzylamine. Also, dimethylnitrosamine may be partly metabolized by enzymes unrelated to the mixed-function oxidase complex. (13 refs.)

- 77-5610 Phenolic Antioxidants and the Inhibition of Hepatotoxicity from *N*-Dimethylnitrosamine Formed In Situ in the Rat Stomach.** (Eng.) Astill, B. D. (Health, Safety, and Human Factors Lab., Eastman Kodak Co., Rochester, NY); Mulligan, L. T. *Food Cosmet Toxicol* 15(3): 167-171; 1977.

The in vivo action of phenolic antioxidants on an *N*-nitrosamine (NOA)-forming system of nitrite and dimethylamine (DMA) was investigated in the rat stomach. After a 12-hr fast, the following were administered by gastric intubation: 1 g/kg DMA and 125 mg/kg sodium nitrite followed immediately by the test compound in doses of 25, 75, or 225 mg/kg (propyl gallate, PG; butylated hydroxyanisole, BHA; butylated hydroxytoluene, BHT; and tert-butylhydroquinone, TBHQ). Sodium ascorbate (200 mg/kg) was used as a positive control. Although concentrations that inhibited NOA formation could not be ascertained directly, (because of variable stomach-emptying times), there was an approx equivalence of nitrite and PG or TBHQ concentrations for inhibition of the NOA-forming system. Inhibition by PG or TBHQ was dose-related, and in this respect these compounds are similar to ascorbate. The PG or TBHQ/nitrite concentration ratios were lower than those presumably required to inhibit NOA formation, but the ratios for all four compounds tested were close to those at which no effects on the NOA-forming system were encountered. It is concluded that under normal usage conditions, phenolic antioxidants would be unlikely to promote NOA formation in the stomach and that under conditions of low or diminished nitrite intake, PG and TBHQ might inhibit any NOA formation completely. (21 refs.)

- 77-5611 Selective Induction of Intestinal Tumors in Rats by Methyl(acetoxymethyl)nitrosamine, an Ester of the Presumed Reactive Metabolite of Dimethylnitrosamine.** (Eng) Joshi, S. R. (Div. Anti-Infective Drug Products, Bureau Drugs, Federal Drug Admin., 5600 Fishers Lane, Rockville, MD 20852); Rice, J. M.; Wenk, M. L.; Roller, P. P.; Keefer, L. K. *J Natl Cancer Inst* 58(5): 1531-1535; 1977.

Methyl(acetoxymethyl)nitrosamine (DMN-OAc) was syn-

thesized and assayed for toxicity and carcinogenicity in rats to test the hypothesis that α -hydroxylation is required for metabolic activation of dimethylnitrosamine (DMN) to a reactive, proximate carcinogen. The acute LD50's of DMN-OAc and DMN injected ip into 5-wk-old male Sprague-Dawley rats were 25 and 44 mg/kg, respectively. Single ip injections of one-half the LD50 of DMN-OAc in 5-wk-old rats of both sexes resulted in a high incidence of epithelial tumors of the intestinal tract. Mean survival times for rats with intestinal tumors were 353 days for males and 433 days for females. Tumors were rarely found at other sites. DMN at equivalent toxic (22 mg/kg) and molar (7.0 mg/kg) doses yielded tumors of the kidneys, lungs, and, occasionally, other organs, but at a much lower incidence. The high toxicity and potent carcinogenicity of DMN-OAc are consistent with the hypothesis that the deacetylated derivative methyl(hydroxymethyl)nitrosamine (DMN-OH) is the reactive metabolite responsible for tissue damage and carcinogenesis by DMN. Tissue damage by DMN probably occurs in cells in which the reactive intermediate is formed, because the lability of DMN-OH precludes diffusion to distant sites. The organotropism of DMN-OAc is different from that of DMN because DMN-OH is generated by the two compounds by different metabolic paths. (10 refs.)

77-5612 Fibrinolytic Activity Associated with Rat Brain Cells Exposed Transplacentally to the Carcinogen Ethylnitrosourea (Meeting Abstract). (Eng.) Hince, T. A. (Dept. Cell Pathology, Sch. Pathology, Middlesex Hosp. Medical Sch., London, England); Roscoe, J. P. *Br J Cancer* 36(3): 401-402; 1977. (3 refs.)

77-5613 An Investigation of Ethylnitrosourea-induced Carcinogenesis in the Rat Brain by an In Vivo-In Vitro Method (Meeting Abstract). (Eng.) Roscoe, J. P. (Dept. Cell Pathology, Sch. Pathology, Middlesex Hosp. Medical Sch., London, England); Claisse, P. J. *Br J Cancer* 36(3): 401; 1977. (1 ref.)

77-5614 Prenatal Induction by ENU of Focal Hepatic Glycogenesis and Hepatocellular Tumors in Mice (Meeting Abstract). (Eng.) Bannasch, P. (Abt. Cytopathologie, Inst. Experimental Pathology, Deutsches Krebsforschungszentrum, D-6900 Heidelberg, W. Germany); Venske, G.; Mayer, D. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 82; 1977. (no refs.)

77-5615 Phenotypic Properties of Neoplastic Cell Lines Developed from Fetal Rat Brain Cells in Culture after Exposure to Ethylnitrosourea In Vivo. (Eng.) Laerum, O. D. (Dept. Pathology, Gade Inst., Univ. Bergen, N-5000 Bergen, Norway); Rajewsky, M. F.; Schachner, M.; Stavrou, D.; Haglid, K. G.; Haugen, A. *Z Krebsforsch* 89(3): 273-295; 1977.

Fetal BD IX rat brain cells (FBC), transferred to long-term culture after a transplacental pulse of N-ethyl-N-nitrosourea (EtNU) on the 18th day of gestation, underwent neoplastic transformation in vitro (BT cell lines). The properties of these lines and the histologic appearance of the tumors obtained by the sc reimplantation of BT cells into baby BD IX rats were studied. Histologically, the tumors resembled neurinomas, gliomas, glioblastomas, and undifferentiated pleomorphic neoplasms. In spite of atypical cellular morphology, these tumors grossly resembled the different types of neuroectodermal rat neoplasms induced by EtNU in vivo. Like the neoplastic cell culture lines derived from EtNU-induced, neuroectodermal BD IX rat tumors ("V cell lines"), the BT lines contained multipolar glialike cells; flat cells with fewer and shorter cytoplasmic processes, and some giant cells were also seen. Both the V and BT lines showed different levels of aneuploidy. They contained multiple subpopulations of cells, as reflected by plurimodal pulse-cytophotometric DNA distributions. All lines contained varying amounts of the nervous system specific protein S-100, a marker not yet expressed in FBC. There was no indication of more than borderline neurotransmitter activity, suggesting that proliferating (precursor) cells of glial lineages may preferentially undergo malignant transformation after exposure to EtNU during this stage of brain development. (45 refs.)

77-5616 Effect of Split Doses of N-Methyl-N-nitrosourea on DNA Repair Synthesis in Cultured Mammalian Cells. (Eng.) Zardi, L. (International Agency for Res. on Cancer, 150 Cours Albert Thomas, 69008 Lyon, France); St. Vincent, L.; Barbin, A.; Montesano, R.; Margison, G. P. *Cancer Lett* 3(3-4): 183-188; 1977.

DNA repair synthesis was investigated in confluent monolayers of human fibroblasts, mouse C3H 10T1/2 fibroblasts, and rat hepatocytes exposed to split doses (125 or 250 μ g/ml) or a single dose (500 μ g/ml) of N-methyl-N-nitrosourea (MNU). DNA repair was determined by unscheduled DNA synthesis as measured by the incorporation of 3 H-thymidine in the presence of hydroxyurea. No significant difference in DNA repair was detected in the three cell lines treated with a single dose or split doses of MNU. (14 refs.)

77-5617 Target Cells of the Leukaemogens Butyl and Methyl Nitrosourea (Meeting Abstract). (Eng.)

Baines, P. (Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester, England). *Br J Cancer* 36(3): 429-430; 1977. (no refs.)

77-5618 **Transformed BHK Cells Exhibiting Normal or Subnormal Sugar Uptake.** (Eng) Moolten, F. L. (Dept. Microbiology, Boston Univ. Sch. Medicine, Boston, MA 02118); Moolten, D. N.; Capparell, N. J. *J Cell Physiol* 93(1): 147-152; 1977.

Deoxyglucose uptake was compared in BHK cells and in DMN4B cells, a conditionally transformed BHK cell line that exhibits transformed behavior at 38.5 C but not at 32 C. At 32 C, DMN4B cells took up deoxyglucose more slowly than BHK cells, reflecting a higher Km for uptake of this sugar. At 38.5 C, the Km for DMN4B cells was reduced to a level only slightly greater than that for BHK cells, and deoxyglucose uptake was similar in the two cell lines. Growth in glucose-free medium for 22 hr stimulated deoxyglucose uptake in both BHK and DMN4B cells; under these conditions, uptake was equal in the two cell lines, both at 32 C and 38.5C. Glycolysis, measured by lactic acid production, was slower in DMN4B than in BHK cells, but this difference was observed at 38.5 C, rather than 32 C. That the subnormal deoxyglucose uptake of DMN4B cells in the untransformed state (32 C) can be normalized by growth at 38.5 C, a temperature permissive for transformation, suggests that membrane changes facilitating sugar uptake are associated with transformation in DMN4B cells. However, the failure of uptake to exceed normal in these cells indicates that their transformed behavior is not attributable to excessive sugar uptake per se. (24 refs.)

77-5619 **Sensitivity to Nitrosomethylurea of Embryonal Lung Cells of Mice, Rats, and Man in Organ Cultures.** (Rus.) Kolesnichenko, T. S. (Dept. Carcinogenic Agents, Oncological Res. Center, Acad. Medical Sciences USSR, Moscow, USSR.). *Biull Eksp Biol Med* 84(9): 349-352; 1977.

The sensitivity of lung cultures from humans, A line mice, and Wistar rats to nitrosomethylurea (NMU: 0.05 mg/ml) was studied. The tissues were cultured in the presence of NMU for 15 days, during which time the NMU was replaced at 2- to 3-day intervals, and then cultured without NMU. NMU had a marked toxic effect on human and rat embryonal tissues; the percentages of cells with degenerative changes were 84.6 and 88.6, respectively, on the 8th day, but the effect failed to intensify with time. NMU had no toxic effect on mouse lung cultures. Reduction of the percentages of degenerative cellular changes in the human and rat lung cultures by the 15th day indicated a reduction in sensitivity to NMU. Survival of the tissue explants was longer than that of control tissue. Hyperplastic (diffuse-focal) proliferation of the alveolar and bronchial epithelium was most pronounced in the

mouse lung cultures, least marked in the human lung tissue. The frequency of these changes showed a similar pattern. The findings indicate a similarity of the preneoplastic and neoplastic changes induced by NMU in human and rodent organ cultures in vitro. (14 refs.)

77-5620 **Reversal by Vitamin A Analogues (Retinoids) of Hyperplasia Induced by N-Methyl-N'-nitro-N-nitrosoguanidine in Mouse Prostate Organ Cultures.** (Eng.) Chopra, D. P. (Kettering-Meyer Lab., Southern Res. Inst., Birmingham, AL 35205); Wilkoff, L. J. *J Natl Cancer Inst* 58(4): 923-930; 1977.

The antihyperplastic activity of β -retinoic acid (RA) and nine synthetic analogs (retinoids) was examined in organ cultures of mouse prostate made hyperplastic by treatment with 1 μ g/ml N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). After 8 or 10 days, when most explants from C3H or (C57BL x DBA)F₁ mice developed hyperplasia, the carcinogen was withdrawn and explants were incubated in a control medium and medium containing different concentrations of a retinoid. Different retinoids produced variable degrees of mitotic inhibition in the hyperplastic prostate epithelium. The methylketocyclopentenyl and 1-methoxyethylcyclopentenyl analogs of RA were at least fiftyfold more active than RA in reversing MNNG-induced hyperplasia. The trimethylmethoxyphenyl analog and retinyl methyl ether were significantly more active than RA. Three analogs, N-acetylretinylamine, retinal acetyl hydrazone, and retinal oxime, were as active as RA. The chlorotrimethylphenyl analog was less active, and the α -retinyl acetate was completely devoid of mitotic inhibitory activity. (26 refs.)

77-5621 **Morphometric Investigations on Experimentally Induced Adenocarcinoma of the Glandular Stomach of the Rat (Meeting Abstract).** (Ger.) Roessner, A. (Munster, Westfalen, W. Germany); Uchida, Y.; Schlake, W.; Stahl, K. *Zentralbl Allg Pathol* 121(3): 297-298; 1977. (no refs.)

77-5622 **Spontaneous, Chemical and Viral Mutagenesis in Temperature-sensitive Glutamine-requiring Chinese Hamster Cells.** (Eng) Varshaver, N. B. (Kurchatov Inst. Atomic Energy, Moscow, USSR); Marshak, M. I.; Luss, E. V.; Gorbunova, L. V.; Shapiro, N. I. *Mutat Res* 43(2): 263-278; 1977.

A mutant cell clone of Chinese hamster cells exhibiting glutamine requirements at a high temperature (40.3 C) was used to study various problems of mutagenesis in cultured mammalian cells. The spontaneous rate of reversions to glutamine

prototrophy, as determined by the fluctuation test, varied from $0.83-3.64 \times 10^{-6}$ per cell per generation in three experiments. Glutamine-dependent temperature-sensitive (Glu-^{ts}) cells were treated with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), and the frequency of induced revertants was estimated by comparison with control cultures. MNNG significantly increased the yield of revertants. The frequency of revertants was max ($1.3-7.2 \times 10^{-5}$) when the cells were transferred to selective conditions two to three cell generations after mutagenic treatment. With a longer expression time, the yield of back-mutations decreased. Glu-^{ts} cells were also infected with simian virus 40 (SV40) and examined for mutagenesis 2-3 days after infection. In 9/11 experiments, the number of revertants to glutamine independence following infection exceeded their number in a control series. It is suggested that the mutagenic effect of SV40 is not locus-specific and that the virus might induce mutations by base-pair substitutions in DNA. It is concluded that this system is particularly useful for quantitative studies of environmental mutagenesis. (30 refs.)

- 77-5623 **Strand Breaks of Mammalian Mitochondrial DNA Induced by Carcinogens.** (Eng.) Miyaki, M. (Dept. Biochemistry, Tokyo Metropolitan Inst. Medical Science, 3-18, Honkomagome, Bunkyo-ku, Tokyo, 113, Japan); Yatagai, K.; Ono, T. *Chem Biol Interact* 17(3): 321-329; 1977.

Strand breakage of Ah66 Rat ascites cell and HeLa S3 cell mitochondrial DNA induced by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and 4-nitroquinoline 1-oxide (4NQO) was investigated. The cells were incubated with the carcinogens at 37 C for 30 to 60 min. The closed circular DNAs of the two lines were degraded to open circular forms, with the MNNG causing more strand scission than 4NQO at the same concentration. Nuclear DNA synthesis was inhibited more by 4NQO than by MNNG. The recovery of mitochondrial DNA synthesis paralleled that of nuclear DNA synthesis. Nuclear DNA synthesis inhibited by 4NQO was not restored, and fragmented DNA was not repaired. (16 refs.)

- 77-5624 **Effects of the Water-soluble Carcinogen 4-Nitroquinoline N-Oxide on Hamster Lingual Mucosa.** (Eng.) Eveson, J. W. (Dept. Pathology, Royal Dental Hosp. London, Sch. Dental Surgery, London, WC2, England); MacDonald, D. G. *Oral Surg* 44(4): 600-605; 1977.

The water-soluble carcinogen 4-nitroquinoline N-oxide (4NQO, 0.09 mg/animal) was applied to the ventral lingual mucosa of 15 male Syrian hamsters twice weekly for up to 20 wk. No neoplasms developed during this period. The promoting agent croton oil was then applied to the treated areas to determine whether initiation had occurred. During the fol-

lowing 6 mo, one animal developed a papilloma and three showed areas of epithelial atypia in the treated mucosa. No malignant neoplasms were seen. These results contrast with the efficiency of 4NQO in inducing intraoral neoplasms in the rat. (22 refs.)

- 77-5625 **Metabolic Reduction of 4-Nitroquinoline N-Oxide and Other Radical-producing Drugs to Oxygen-reactive Intermediates.** (Eng.) Biaglow, J. E. (Div. Radiation Biology, Dept. Radiology, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH 44106); Jacobson, B. E.; Nygaard, O. F. *Cancer Res* 37(9): 3306-3313; 1977.

Factors affecting electron transfer from intracellular reducing agents to 0.1 or 1 M 4-nitroquinoline N-oxide (4NQO), 0.1 or 1 M menadione (MD), and nitrofur derivatives (all at 1 M), as well as reactions of the resulting drug radical intermediates, were investigated. Drug metabolism was studied in Ehrlich ascites tumor cells and V79 Chinese hamster lung cells. All compounds stimulated O₂ consumption of Ehrlich cells in the presence and absence of KCN, but glucose was necessary for max stimulation. The increased consumption of O₂ was due to the production of radical intermediates. Evidence for the radical intermediate of 4-NQO was obtained by measuring the reduction of intracellular ferricytochrome c + c₁ with or without inhibition of early steps of the cytochrome chain. Blockage of cytochrome oxidase by KCN, which also inhibits catalase and superoxide dimutase, resulted in transfer of the radical anion electron to O₂, with the production of O₂ superoxide and peroxide. Production of the latter also occurred with MD and nitrofurazone. The O₂ superperoxide radical and peroxide were also produced with isolated microsomes in the presence of 4-NQO, nitrofurazone, and MD. Neither cell suspensions nor isolated microsomes reduced the nitrofurans to stable intermediates in the presence of O₂. However, 4-NQO was reduced to the corresponding hydroxylamino derivative in aerobic suspensions of both Ehrlich and V79 cells. The reaction depended on reducing substrates (NADPH or glutathione) and was stimulated by KCN and anoxia. With V79 cells, metabolic activation of 4-NQO was found to be necessary for its cytotoxicity. KCN-inhibited mammalian cells in suspension may be useful for studying the production of radical intermediates in the metabolism of certain nitro compounds known to be potential mutagens and carcinogens. (36 refs.)

- 77-5626 **Nonuniform Distribution of DNA Repair in Chromatin after Treatment with Methyl Methanesulfonate.** (Eng.) Bodell, W. J. (Tumor Biology Lab., Sch. Life Sciences, 201 Lyman Hall, Univ. Nebraska, Lincoln, NB 68588). *Nucleic Acids Res* 4(8): 2619-2628; 1977.

Micrococcal nuclease digestion was used to examine the distribution of DNA repair in chromatin isolated from BALB/c

mammary glands following treatment with 3 milliM methyl methane sulfonate (MMS). The results indicate that there is a nonuniform distribution of DNA repair in the chromatin. The region of chromatin digested during the first 5 min of incubation with micrococcal nuclease apparently is a primary site for DNA repair after MMS treatment. The nonuniform distribution of DNA repair may be due to a nonuniform alkylation of DNA in the chromatin by MMS or a uniform base alkylation, or to regions of chromatin having an increased accessibility for the repair enzymes to the DNA lesions. The resulting presence of unrepaired DNA lesions in the genome may be an important event in mutagenesis, carcinogenesis, and cellular aging. (46 refs.)

- 77-5627 **Effects of Six Carcinogens on SCE Frequency and Cell Kinetics in Cultured Human Lymphocytes.** (Eng.) Craig-Holmes, A. P. (Medical Genetics Center, Graduate Sch. Biomedical Sciences, Univ. Texas Health Science Center at Houston, Houston, TX 77025); Shaw, M. W. *Mutat Res* 46(5): 375-384; 1977.

The effects of methylmethanesulfonate, ethylmethanesulfonate, dimethylnitrosamine (DMN), diethylnitrosamine (DEN), benzo(a)pyrene and mitomycin C on sister chromatid exchanges and cell kinetics were investigated in asynchronously dividing lymphocyte cultures. With the exception of DMN and DEN, the carcinogens had a significant effect on both these parameters; this effect was dependent on both concentration and length of exposure. (34 refs.)

- 77-5628 **Mechanisms of Chromatid Breakage in Human Lymphocyte Cultures.** (Eng.) Meisner, L. F. (Cytogenetics Unit, State Lab. Hygiene, Univ. Wisconsin, Madison, WI); Chuprevich, T. W.; Inhorn, S. L. *Acta Cytol (Baltimore)* 21(4): 555-558; 1977.

Spontaneous and induced chromatid breakage were investigated in lymphocyte cultures from four blood donors. Chromosome protein modifications as a result of exposure to actinomycin D and other chemicals after DNA synthesis can result in breaks in susceptible regions. Therefore, human cultures being assessed for mutagenesis must be scored for rearrangements reflecting DNA damage and repair and not chromatid breakage alone. (20 refs.)

- 77-5629 **Effect of Caffeine on Sister Chromatid Exchanges and Chromosomal Aberrations Induced by Mutagens in Chinese Hamster Cells.** (Eng.) Palitti, F. (Centro di Genetica Evoluzionistica del C.N.R., Citta Universitaria, 00185 Rome, Italy); Becchetti, A. *Mutat Res* 45(1): 157-159; 1977.

The effect of caffeine (10^{-3} M) on mutagen-induced sister chromatid exchanges (SCE) and chromosome aberrations was studied in a diploid Chinese hamster cell line. The mutagens were ethyl methanesulfonate (10^{-3} M), methyl methane-sulfonate (10^{-5} M), dimethyl sulfonate (10^{-5} M), 4-nitroquinoline 1-oxide (10^{-5} M), mitomycin C (10^{-6} M), and thiotepa (10^{-6} M). Caffeine strongly increased the frequency of mutagen-induced chromosome aberrations but not the frequency of mutagen-induced SCE. It is concluded that there is no close relationship between the processes leading to SCE and chromosome aberrations and that SCE do not result from a caffeine-sensitive postreplication repair of DNA damage. (17 refs.)

- 77-5630 **Analysis of Karyotype Variation Following Carcinogen Treatment of Chinese Hamster Primary Cell Lines.** (Eng.) Connell, J. R. (Chemical Carcinogenesis Div., Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks. HP8 4SP, England); Ockey, C. H. *Int J Cancer* 20(5): 768-779; 1977.

Chinese hamster primary embryo fibroblasts were treated with the carcinogens benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene or N-methyl-N'-nitro-N-nitrosoguanidine. Karyotype analysis, sister chromatid exchange frequency, evidence of transformation by growth in agar, cell morphology, and reaction to cytochalasin B were tested at regular intervals over many culture passages. Carcinogen treatment shortened the time before onset of permanent karyotypically changed stem and side lines and in vitro transformation. Chromosomes X, 6, and 10 were involved in the majority of cultures expressing permanent chromosome changes. Spontaneous chromatid aberrations and aneuploidy increased in frequency with time in culture and generally appeared prior to the expression of transformation. No specific chromosomes were involved with the different carcinogens. There was no correlation between in vitro transformation and karyotype evolution, and the criteria for transformation were present independently of one another. The lack of correlation between the parameters tested suggests that the expression of in vitro transformation is a result of selection for growth advantage from a cell population expressing an increasing degree of genetic instability and variation with time in culture. (36 refs.)

- 77-5631 **Chromosomal Effects of Carcinogens and Non-carcinogens on WI-38 after Short Term Exposure with and Without Metabolic Activation.** (Eng.) Weinstein, D. (Dept. Experimental Pathology, Hoffmann La Roche Inc., Nutley, NJ 07110); Katz, M. L.; Kazmer, S. *Mutat Res* 46(4): 297-303; 1977.

Cultured WI-38 human diploid fibroblasts were analyzed for chromosome damage after 24-hr exposures to benzo(a)pyrene

(BP), 3-methylcholanthrene (MC), N-methyl-N'-nitrosoguanidine (MNNG), 4-nitroquinoline-1-oxide (4NQO), pyrene, and caffeine. A low concentration of 4NQO (0.15 μ M) and MNNG (1.9 μ M) produced breakage and exchange figures. A relatively high concentration of caffeine (1,300 μ M) caused breakage. The other compounds (BP, MC, and pyrene) increased damage only slightly, if at all, above control levels. A 1-hr pulse exposure of WI-38 cells to BP (40 μ M) in the presence of a rat liver homogenate supernate (S-9) resulted in damage significantly greater than in untreated cells or cells treated with BP alone. 4NQO (0.25 μ M) produced exchange figures after a similar 1-hr exposure, but this effect was eliminated by S-9. A concentration of 10-300 μ M caffeine was required to cause breakage greater than control levels after a 1-hr exposure. The results indicate a possible short-term, in vitro, human cell system for distinguishing carcinogens, procarcinogens, and noncarcinogens. (19 refs.)

77-5632 Chemical Mutagenesis Studies with Cultured Mammalian Cells (Meeting Abstract). (Eng.) Malcolm, A. R. (Univ. Rhode Island, Kingston, RI 02881). *Diss Abstr Int [B]* 38(4): 1553; 1977. (no refs.)

77-5633 Studies of Nucleic Acid Chemistry: I. The Solution Structure of Yeast Initiator Transfer RNA Studied by Oligoribonucleotide Binding. II. A Chemical Model of Mutagenesis (Meeting Abstract). (Eng.) Freier, S. M. (Univ. California, Berkeley, CA 94720). *Diss Abstr Int [B]* 38(2): 645; 1977. (1 ref.)

77-5634 Infidelity of DNA Synthesis as Related to Mutagenesis and Carcinogenesis. (Eng.) Loeb, L. A. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111); Sirover, M. A.; Weymouth, L. A.; Dube, D. K.; Seal, G.; Agarwal, S. S.; Katz, E. *J Toxicol Environ Health* 2(6): 1297-1304; 1977.

An assay using homogeneous avian myeloblastosis virus DNA polymerase and poly[d(A-T)] as a template was developed to test the fidelity of DNA synthesis in vitro by measuring simultaneously the rates of incorporation of (α - 32 P)-complementary and 3 H-noncomplementary nucleotides. Following incubation of the reaction mixture for 60 min at 37 C, noncomplementary nucleotides were incorporated as single base substitutions as a result of viral polymerase activity. In a study of 31 metal compounds, the substitution of metal cations Ag^+ , Be^{2+} , Cd^{2+} , Co^{2+} , Cr^{2+} or Cr^{6+} , Mn^{2+} , Ni^{2+} , Pb^{2+} , and Cu^{2+} for Mg^{2+} as the added divalent cation decreased the fidelity of DNA synthesis by > 30%. With the exception of Cu^{2+} , Fe^{2+} , and Zn^{2+} , whose carcinogenicity or mutagenicity are questionable, a positive cor-

relation was observed between the mutagenicity and/or carcinogenicity of these metals in vivo and their enhancement of infidelity in vitro. Thus, this system may be valuable for screening a wide variety of potential carcinogens. (17 refs.)

77-5635 A Review of the Metabolism and Toxicology of Nickel. (Eng.) Sunderman, F. W. (Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT 06032). *Ann Clin Lab Sci* 7(5): 377-398; 1977.

A review of the toxicity, teratogenicity, and carcinogenicity of nickel in animals and man is presented. Nickel has been implicated in soft tissue sarcomas and in carcinomas of the lung, nasal cavities, larynx, kidney and gastric tract. A case of invasive nasal epidermoid carcinoma in a 36-yr-old male factory worker with 5-yr exposure to nickel fumes is reported, and occupational hazards of nickel exposure are reviewed. (177 refs.)

77-5636 Mortality Experience in Relation to a Measured Arsenic Trioxide Exposure. (Eng.) Pinto, S. S. (ASARCO Incorporated, Post Office Box 1677, Tacoma, WA 98491); Enterline, P. E.; Henderson, V.; Varner, M. O. *Environ Health Perspect* 19: 127-130; 1977.

A total of 527 men, all at least 65 yr old, and all having been exposed to airborne arsenic trioxide while working at a copper smelter, were studied for mortality experience. The av airborne arsenic concentration ranged from 3 to 295 μ g/m³ (overall mean 53 μ g/m³) and the av urinary values ranged from 38 to 539 μ g/liter (overall av 174 μ g/liter), showing a good correlation between these concentrations over the range studied. Exposure to arsenic trioxide was reflected in the workers' urine within 24 hr, so that biological monitoring of urinary arsenic could be directly related to airborne arsenic trioxide. The overall mortality rate was 12.2% higher for the study group than for men in the same area. The excess of mortality was due primarily to cancer of the respiratory system, which was 3 times the expected value, with some excess cancer of the digestive system. There was no relationship between cigarette smoking and the respiratory cancer. Notably, cancer of the urinary tract was not increased, which suggests that the body has a successful detoxification mechanism for handling inorganic trivalent arsenic. The risk of lung cancer declined after the workers were removed from arsenic exposure. These results indicate that there is a threshold of safety for arsenic trioxide exposure; however, further analyses of these and other data must be made to establish the level of such a threshold. (8 refs.)

77-5637 Ecological Investigations on Arsenic Dietary Intake and Endemic Chronic Poisoning in Man:

Dose-Response Curve. (Eng.) Zaldivar, R. (2170 N.W. 11th St., Suite 53, Miami, FL 33125). *Zentralbl Bakteriol [Orig B]* 164(5/6): 481-484; 1977.

A dose response curve was constructed based on a study of 220 persons from the city of Antofagasta, Chile, where there is a mean concentration of arsenic in the drinking water of 0.600 ppm. There was a linear relationship between arsenic dose (mg/kg body wt/day) and age. The slope of the dose-response curve was statistically significant; the correlation coefficient was +0.9604. (6 refs.)

77-5638 Effects and Dose-Response Relationships of Skin Cancer and Blackfoot Disease with Arsenic. (Eng) Tseng, W. P. (Dept. Medicine, Natl. Taiwan Univ., Coll. Medicine, Taipei, Taiwan, Republic China). *Environ Health Perspect* 19: 109-119; 1977.

A survey was conducted of 40,421 inhabitants of a limited area on the southwest coast of Taiwan, where artesian well water with a high concentration of arsenic (0.01-1.82 ppm) had been used for > 60 yr. A considerable number of these inhabitants suffered from chronic arsenicism, arsenical skin cancer, or blackfoot disease. The prevalence rates were 10.6/1,000 for skin cancer and 8.9/1,000 for blackfoot disease. The rates for both diseases increased steadily with age and with arsenic content in the well water. A dose-response relationship between blackfoot disease and duration of arsenical water intake was also noted. Furthermore, the severity of impairment of the patient correlated significantly with duration of water intake at the time of onset. The most common type of lesion was intraepidermal carcinoma (51.7%) and the body areas most often involved were unexposed surfaces (74.5%). Multiple skin cancers were extremely high in this series (99.5%). It was found that the association of blackfoot disease with hyperpigmentation, keratosis, or skin cancer was not a chance occurrence, supporting a causal relationship between blackfoot disease and chronic arsenicism. Both skin cancer and blackfoot disease are concluded to be part of the entity of chronic arsenicism. (27 refs.)

77-5639 Chromosome Aberrations in Workers Exposed to Arsenic. (Eng) Beckman, G. (Dept. Medical Genetics, Univ. Umea, Umea, Sweden); Beckman, L.; Nordenson, I. *Environ Health Perspect* 19: 145-146; 1977.

Lymphocytes from nine workers chronically exposed to arsenic at a smelter were cultured for 68-70 hr and examined for chromosome aberrations. Of a total of 819 cells, there were 71 aberrant cells and 87 aberrations, including 56 gaps, 12 chromatid aberrations, and 19 chromosome aberrations. Individual variations ranged from 0 to 25 aberrations per 100 cells. The frequency of aberrant cells was 8.7%, a rate that was significantly higher ($p < 0.001$) than that of control cells

(1.3%). There were 13 aberrant cells and 13 aberrations (9 gaps, 3 chromatid aberrations, and 1 chromosome aberration) in a total of 1,012 control cells. Definitive conclusions regarding the mutagenic-carcinogenic effect of arsenic could not be made, however, because the individual with the highest frequency of aberrations was also exposed to lead and selenium at the smelter. (6 refs.)

77-5640 Effects of Arsenic Cell Metabolism and Cell Proliferation: Cytogenetic and Biochemical Studies. (Eng) Petres, J. (Dept. Clinical and Experimental Dermatology, Univ. Freiburg im Breisgau, Freiburg im Breisgau, W. Germany); Baron, D.; Hagedorn, M. *Environ Health Perspect* 19: 223-227; 1977.

A chromosome analysis was performed on lymphocytes from 14 psoriasis patients and 17 vine growers, who had a history of extensive arsenic contact, and a control group of 31 subjects (14 with psoriasis) who had no history of arsenic exposure. Several of the test group patients had had arsenic-induced skin carcinomas excised. The types of chromosome aberrations/mitoses for the exposed and control group, respectively, were: secondary constrictions, 52/1,121 and 13/1,247; achromatic lesions, 29/1,121 and 3/1,247; gaps, 58/1,121 and 9/1,247; chromatid breaks, 34/1,121 and 1/1,247; acentric fragments, 39/1,121 and 2/1,247; and dicentric chromosome, 3/1,121 and 0/1,247. Radioactive incorporation studies showed that arsenic was able to inhibit, in a dose-dependent manner, the uptake of radioactively-labeled thymidine into RNA and DNA. It also blocked cells in the S and G₂ phases. The inhibitory effect of inorganic arsenic on cell metabolism may be explained by the strong affinity of arsenic for enzymes, especially those containing sulfhydryl groups. (28 refs.)

77-5641 Changes in the Chemical Speciation of Arsenic Following Ingestion by Man. (Eng) Crecelius, E. A. (Battelle, Pacific-Northwest Labs., Marine Res. Lab., Sequim, WA 98382). *Environ Health Perspect* 19: 147-150; 1977.

A semiquantitative analysis was made of the chemical species and excretion rates in urine following ingestion of three species of arsenic by a 30-yr-old man weighing 70 kg. The three substances included arsenite-rich wine (50 $\mu\text{g As}^{+3}$ and 13 $\mu\text{g As}^{+5}$), arsenate-rich well water (200 $\mu\text{g As}^{+5}$), and crab meat (2,000 μg of an organoarsenic compound). Following ingestion of the wine, approx 10% of the arsenic was excreted as arsenite, but most of the arsenic was methylated to methylarsonic acid and dimethylarsinic acid (DMAA) and excreted. Elevated levels of both arsenate and DMAA were seen after ingestion of the water. None of these species was observed following ingestion of the

crab meat until the urine was heated in 2N NaOH, when high levels of DMAA were found. Most of the arsenic was excreted within 85 hr following ingestion; The apparent biological half-lives were 10 hr for inorganic arsenic and 30 hr for the methylated forms. (11 refs.)

- 77-5642 **Ultrastructural and Biochemical Effects of Prolonged Oral Arsenic Exposure on Liver Mitochondria of Rats.** (Eng) Fowler, B. A. (Environmental Toxicology Branch, Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC 27709); Woods, J. S.; Schiller, C. M. *Environ Health Perspect* 19: 197-204; 1977.

Charles River rats were divided into four groups of 18 rats each and given access to deionized drinking water containing 0, 20, 40, or 85 ppm arsenic as sodium arsenate (As^{+3}) for 6 wk. No mortality occurred, and a significant depression in growth rate was observed only in rats receiving 85 ppm. In rats exposed to 40 and 85 ppm, in situ mitochondrial swelling was the most pronounced ultrastructural change, and it was accompanied by lipid droplet formation and fibrosis. At 20 ppm, only occasional cells with swollen mitochondria were seen. Decreased respiratory control ratios and depressed state 3 respiration were seen for pyruvate/malate-, but not for succinate-mediated respiration. These effects were most pronounced in the 40- and 85-ppm groups. P/O ratios were measurably lowered for both succinate and pyruvate/malate substrates only at the 85-ppm dose. The specific activities of monoamine oxidase (MAO) and cytochrome oxidase (CO) were elevated to 150%-200% over controls. MAO activity was increased at all doses, and no dose response was observed. Differences in the activity of CO were significant ($p < 0.01$) at the 20- and 85-ppm levels; $p < 0.05$ at the 40-ppm level. Again, no dose response was observed. Malate dehydrogenase activity remained unchanged at all doses given. The arsenic-mediated disturbance of important enzyme systems responsible for respiration and other mitochondrial functions is a significant manifestation of cellular dysfunction. (21 refs.)

- 77-5643 **Effects of Arsenic on Pyruvate Dehydrogenase Activation.** (Eng) Schiller, C. M. (Lab. Environmental Toxicology, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC 27709); Fowler, B. A.; Woods, J. S. *Environ Health Perspect* 19: 205-207; 1977.

Adult male Charles River rats were given deionized drinking water containing 0, 20, 40, and 85 ppm arsenic as sodium arsenate (As^{+3}) for 3 and 6 wk. The pyruvate dehydrogenase (PDH) activities were then determined by the stoichiometric release of ^{14}C -labeled CO_2 from pyruvate in liver homogenates from these rats. Exposure to the three dose levels for 3 wk decreased basal PDH activity 20%, 23%, and 48%, respec-

tively, and total PDH activity 14%, 15%, and 28%, respectively. After 6 wk of arsenic exposure, basal and total PDH activities were inhibited, but not at the highest dose level. This effect probably reflects mitochondrial regeneration at this time and dose. The possible metabolic effects of this inhibition of PDH activity are discussed. (12 refs.)

- 77-5644 **The Biologic Response to Titanium Phosphate. A New Synthetic Mineral Fiber.** (Eng.) Gross, P. (Dept. Pathology, Medical Univ. South Carolina, Charleston, SC); Kociba, R. J.; Sparschu, G. L.; Norris, J. M. *Arch Pathol Lab Med* 101(10): 550-554; 1977.

The carcinogenicity of titanium phosphate was evaluated by intratracheal and ip injection of the fiber in Sherman strain albino rats and Syrian golden hamsters. In rats, a slight fibrogenic response was observed after intratracheal injection of 50 and 10 mg/kg doses; this was not observed with lower doses or with ip doses. These fibers did not resemble asbestos fibers, which caused abdominal tumors in 34% of rats given 2 mg/kg ip. No abdominal tumors were induced in hamsters after injection of either fiber. (7 refs.)

- 77-5645 **Asbestos Effusion (Meeting Abstract).** (Eng.) Epler, G. R. (Boston, MA); Gaensler, E. A. *Chest* 72(3): 399; 1977. (no refs.)

- 77-5646 **Quantitation of Asbestos-induced Hyperplasia in Hamster Trachea Epithelium Maintained in Organ Culture (Meeting Abstract).** (Eng.) Frank, A. L. (City Univ. New York, New York, NY 10021). *Diss Abstr Inst [B]* 38(4): 1512; 1977. (no refs.)

- 77-5647 **Leaching of Chrysotile Asbestos in Human Lungs: Correlation with In Vitro Studies Using Rabbit Alveolar Macrophages.** (Eng) Jaurand, M. C. (Laboratoire de Biopathologie Pulmonaire, Université Paris Val de Marne, C.H.U. Henri Mondor, Avenue De Lattre De Tassigny, 94010 Creteil, France); Bignon, J.; Sebastien, P.; Goni, J. *Environ Res* 14(2): 245-254; 1977.

Chrysotile fibers from human lungs and from chrysotile phagocytosed in vitro by rabbit alveolar macrophages (AM) were microanalyzed chemically with an energy dispersive spectrometer mounted on a scanning electron microscope (SEM). This microanalysis was also applied to natural fibers to determine the chemical stability of chrysotile in biologic residence. The Mg vs Si content was estimated by the

ratio of their peak intensity. Lung samples were obtained from workmen with definite asbestos exposure, and chrysotile asbestos was extracted by chemical digestion. Phagocytosed chrysotile fibers were obtained after incubating standard chrysotile with rabbit AM for 24 hr or 5 days. Chrysotile fibers from human lungs and from in vitro incubation with AM had an increased Si:Mg ratio compared with standard fibers. Moreover, Mg leakage was not constant along the fiber axis and varied from one fiber to another. (14 refs.)

77-5648 Possible Carcinogenic Effects of Cedar Shavings in Bedding of C3H-AvyfB Mice. (Eng.) Vlahakis, G. (Gene Regulation Section, Lab. Molecular Biology, NCI, NIH, Public Health Service, U.S. Dept. Health, Education, and Welfare, Bethesda, MD 20014) *J Natl Cancer Inst* 58(1): 149-150; 1977.

C3H-AvyfB mice were maintained on bedding consisting of low-resin pine sawdust (37 animals) or on bedding of pine plus cedar shavings (32 animals). The incidence of mammary tumors and hepatomas was high in both groups, with a slightly lower incidence (82% vs 87%) and a slightly higher average (17 vs 16 mo) for the females on the bedding of pine plus cedar. The results indicate that the high incidence of spon-

taneous tumors in C3H-AvyfB mice is not due to the routine use of cedar shavings in bedding materials. (12 refs.)

See also:
*(Rev.): 77-5401, 77-5402, 77-5403, 77-5404, 77-5405, 77-5406, 77-5407, 77-5408, 77-5409, 77-5410, 77-5411, 77-5412, 77-5413, 77-5414, 77-5415, 77-5416, 77-5417, 77-5418, 77-5426, 77-5427, 77-5431, 77-5432, 77-5435, 77-5445, 77-5449, 77-5451, 77-5452, 77-5459, 77-5460, 77-5461.
*(Phys.): 77-5651, 77-5657, 77-5668, 77-5670, 77-5672, 77-5673, 77-5680, 77-5681.
*(Viral): 77-5747, 77-5753, 77-5765, 77-5775, 77-5782.
*(Immun.): 77-5854, 77-5855, 77-5863, 77-5866, 77-5869, 77-5873, 77-5886, 77-5893.
*(Path.): 77-5909, 77-5919, 77-5920, 77-5921, 77-5922.
*(Epid.-Biom.): 77-5939, 77-5943, 77-5944, 77-5945, 77-5946, 77-5947, 77-5949, 77-5951, 77-5953, 77-5954, 77-5955, 77-5956, 77-5958.

PHYSICAL CARCINOGENESIS

- 77-5649 **γ -Ray Mutagenesis of Cultured Mammalian Cells In Vitro and In Vivo.** (Eng.) Suzuki, N. (Section Experimental Radiotherapy, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Okada, S. *Mutat Res* 43(1): 81-90; 1977.

An in vitro assay system used to study the reversion of mouse leukemia L5178Y-Ala32 cells from alanine auxotrophy to prototrophy was adapted to allow for a comparison of γ -ray induced mutations in vivo and in vitro. In vitro cell suspensions were given varying doses at rates of 0.2, 0.56, 2.0, and 50 rads/min. A total of 2.0×10^7 cells were injected ip into BD2 F₁ male mice (8-12 wk old) and then irradiated in vivo (at 50 or 0.2 rads/min) on the 11th day after injection. The expression time of induced mutations was 2 days (after 200 rads) in vitro and 5 days in vivo (in vivo radiation followed by in vitro expression). With respect to both mutation frequency and cell killing, cells grown in vivo were more radioresistant than those grown in vitro. This lower mutation frequency and delayed expression may be due to hypoxia and/or other unknown in vivo conditions. A dose-response curve was cumulative for the in vitro experiments and linear for the in vivo experiments. Sensitization of γ -ray-induced mutations could be demonstrated when cells were treated with bromodeoxyuridine (10^{-6} M) for 15 hr. (25 refs.)

- 77-5650 **Gamma-Radiation-induced Chromosomal Aberrations in Human Lymphocytes: Dose-Rate Effects in Stimulated and Non-stimulated Cells.** (Eng.) Liniecki, J. (Medical Res. Center, Div. Nuclear Medicine and Radiobiology, Sch. Medicine, Lodz, Poland); Bajerska, A.; Wyszynska, K.; Cisowska, B. *Mutat Res* 43(2): 291-304; 1977.

Stimulated and nonstimulated human peripheral blood lymphocytes from healthy adults were irradiated acutely and chronically to test the hypothesis that differences in effects after protraction of a constant dose of low-linear energy transfer (LET) radiation were due to the stage of the cell-cycle (G_0 or G_1) in which the lymphocytes had been irradiated. Four variants of irradiation conditions were applied: irradiation of (1) venous whole blood, (2) oxygenated whole blood, (3) phytohemagglutinin-stimulated (PHA+) culture, and (4) nonstimulated culture (PHA-). Dose-effect relationships for dicentric chromosomes were established, and various models were fitted to the data. The data obtained in PHA- cells basically confirmed the correctness of the classical linear-quadratic model of exchange aberration induction by low-LET ionizing radiation. The yield decreased upon prolonged irradiations, in agreement with the linear-quadratic model of aberration induction. Dose-protraction

experiments showed that the rejoining time increased from about 3 hr in nonstimulated cells to about 10 hr after PHA stimulation. This retarded rejoining is most likely due to blast transformation itself and not to other irradiation conditions. (22 refs.)

- 77-5651 **The Induction of Mutations to 2-Thioxanthine Resistance in Inhibitor Depleted Conidia of *Aspergillus nidulans* by γ -Radiation in the Presence of Oxygen or Nitrogen.** (Eng.) Scott, B. R. (Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709); Alderson, T.; Papworth, D. G. *Mutat Res* 45(1): 21-30; 1977.

The inactivating and mutagenic effect of ^{60}Co -rays on *Aspergillus nidulans* was studied in the presence of oxygen and nitrogen. In the 2-thioxanthine detection system, there was a marked differential in the forward mutation response, dependent on whether the dose was administered in oxygen or nitrogen; this effect was independent of radiation dose. The oxygen enhancement ratios and type of damage induced in the presence of both gases are discussed. (11 refs.)

- 77-5652 **The Effect of Dose Fractionation on γ -Radiation Induced Mutations in Mammalian Cells.** (Eng.) Asquith, J. C. (Environmental and Medical Sciences Div., AERE Harwell, Oxfordshire OX11 0RA, England). *Mutat Res* 43(1): 91-100; 1977.

A V79-4 subline of Chinese hamster lung fibroblasts was exposed to varying single and fractionated doses of ^{60}Co γ -radiation at dose rates of 1.2 and 105 rads/sec. Induced mutation frequency, expressed by resistance to $7.5 \mu\text{g}/\text{cm}^3$ 8-azaguanine, was less after cells received a conditioning dose of about 800 rads followed 6 hr later by a series of graded doses than if radiation was given in a single exposure. Investigation of the effect of increasing the number of fractions in which a fixed dose of 834 rads was given revealed a constant relationship between mutation and survival. In addition, damage to repair systems appeared to be less when a total dose of 834 rads was given in 12 fractions of 69.5 rads than when it was given in six fractions of 139 rads. A mutation response curve was linearly dependent on dose only up to about 300 rads. Cell survival was unaffected by the difference in dose rates between the two sources used. (15 refs.)

- 77-5653 Postradiation Osteosarcoma of the Cervical Spine in Childhood. A Case Report.** (Eng) Dowdle, J. A. (Univ. Minnesota, Dept. Orthopedic Surgery, Mayo Memorial Building, 420 Delaware St. S.E., Minneapolis, MN 55455); Winter, R. B.; Dehner, L. P. *J Bone Joint Surg [Am]* 59-A(7): 969-971; 1977.

The case report of a 14-yr-old girl who developed osteosarcoma 11 yr after ^{60}Co irradiation of the cervical spine for residual grade-I pilocytic astrocytoma and 3 yr after spine fusion for a progressive kyphoscoliosis is presented. The radiation had been delivered posteriorly through a 12 x 6 cm portal; total estimated dose was 4,500 rads. (8 refs.)

- 77-5654 Radiotherapy-induced Osteosarcoma after Successful Treatment of Lung Cancer.** (Eng) Tewfik, H. (Dept. Radiation Therapy, C-142, Univ. Iowa Hosps. and Clinics, Iowa City, IA 52242); Tewfik, F.; Latourette, H.; Christie, J. *Radiology* 125(2): 503-504; 1977.

A 45-yr-old man developed osteosarcoma of the third through fifth ribs as a result of successful radiation treatment for lung cancer. A total tumor dose of 6,000 rads to the midplane was given in a split course. In the first course, ^{60}Co teletherapy was used, and 2,325 rads at Dmax were administered to two parallel fields. In the second course, Betatron 10-million electron volt x-rays were used and the total Dmax for each field was 2,270 rads. (12 refs.)

- 77-5655 Induction of Osteosarcomas and Hematopoietic Neoplasms by ^{55}Fe in Mice.** (Eng) Laissue, J. A. (Kantonsspital Luzern, Inst. Pathology, 6000 Lucerne, Switzerland); Burlington, H.; Cronkite, E. P.; Reincke, U. *Cancer Res* 37(10): 3545-3555; 1977.

Female C57BL/6J mice, aged 10-14 wk, received a single iv injection of $^{55}\text{FeCl}_3$ of high specific activity or equivalent amounts of cold iron. The animals were kept for the duration of their life span to study the late effects of ^{55}Fe . This strain was selected because of its low tumor incidence and long life expectancy. The median survival times after treatment with 2.8, 1.4, and 0.7 mCi ^{55}Fe were 27, 117, and 439 days, respectively. Median survival in controls was > 700 days. No tumors occurred in mice that survived < 300 days. Six osteosarcomas developed in 14 mice that survived ^{55}Fe treatment for > 300 days. In addition, 6 other neoplasms were diagnosed: 2 leukemias, 2 thymic lymphomas, 1 heman-gioendothelioma, and 1 reticulum cell neoplasm. Control mice had not reached their median survival time by posttreatment day 700, and the only tumor noted was a reticulum cell neoplasm. Radioiron was autoradiographically demonstrated in bone surfaces, bone marrow macrophages, and endosteal cells. Osteosarcomas are believed to originate in the endos-

teum; it is possible, therefore, that deposition within the target cell of ^{55}Fe , with its precisely located Auger electron radiation, was instrumental in inducing neoplasms. Alternatively, sufficient radiation for tumor induction may have been accumulated by the x-ray component of bone surface-seeking ^{55}Fe . (21 refs.)

- 77-5656 Histochemistry of Normal Lungs and ^{210}Po Induced Pulmonary Tumors in Hamsters.** (Eng.) Kennedy, A. R. (Dept. Physiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA 02115); Little, J. B. *Acta Histochem Bd* 58(2): 353-359; 1977.

Enzyme studies were conducted on frozen sections of normal lung tissue and lung tumors induced in male Syrian golden hamsters with seven weekly intratracheal instillations of 0.1 μCi ^{210}Po in saline. Elevated levels of lactate dehydrogenase, succinic dehydrogenase, malate dehydrogenase, and acid and alkaline phosphatase were found in the tumor region and bronchiolar Clara cells in the tumor-containing lungs. In the normal lung, Clara cells showed essentially none of these activities. These results, together with previous results from serial-sacrifice experiments, support the hypothesis that these tumors originate from Clara cells. (20 refs.)

- 77-5657 Histochemical, Light and Electron Microscopic Study of Polonium-210 Induced Peripheral Tumors in Hamster Lungs: Evidence Implicating the Clara Cell as the Cell of Origin.** (Eng) Kennedy, A. R. (Dept. Physiology, Harvard Sch. Public Health, Boston, MA 02115); McGandy, R. B.; Little, J. B. *Eur J Cancer* 13(11): 1325-1340; 1977.

Peripheral lung tumors induced in Syrian golden hamsters by intratracheally administered polonium-210 are similar to the peripheral lung tumors induced in many species by a variety of carcinogens. In addition, they show many of the histopathological features observed in human bronchiolar-alveolar carcinomas. Serial-sacrifice studies of hamsters exposed to multiple instillations of ^{210}Po (0.1 μCi) were made to identify the cell of origin of these tumors. Using thin, plastic (glycol methacrylate) sections, electron microscopy, and histochemistry, it was shown that the bronchiolar Clara cell is the probable cell of origin. This view is generally compatible with many of the reported cytological characteristics of the human tumor. (81 refs.)

- 77-5658 Polonium and Plutonium in an Intertidal Food Chain.** (Eng) Cheng, L. (Scripps Institution

Oceanography, Univ. California, La Jolla, CA 92093); Hodge, V. F.; Lewin, R. A. *Nature* 269(5631): 795-796; 1977.

The possibility that polonium and plutonium from kelp may find their way into a terrestrial food chain via kelp flies and beetles was investigated. When the food chain from the kelp to the flies was analyzed, the Po/Pu ratio remained unchanged, and there was no enrichment of the radionuclides. On the basis of current radiation thresholds for human health and safety, there is no hazard from this source of radioactivity. (5 refs.)

77-5659 Plutonium in Bone: A High Resolution Autoradiographic Study Using Plutonium-241. (Eng) Priest, N. D. (Natl. Radiological Protection Board, Harwell, Didcot, Oxon, England); Jackson, S. *Int J Radiat Biol* 32(4): 325-350; 1977.

A plutonium-241 citrate solution, pH 6.5, was injected iv into hamsters and an adult rabbit at a dose of 260 nanoCi/g. The hamsters were killed serially at 15 min, 2 hr, 1 day, 10 days, 1 mo, and 6 mo after injection and the rabbit at 1 wk. Their knee joints or femora were examined for ^{241}Pu by autoradiography. Few differences were found between the pattern of plutonium distribution in the hamsters and the rabbit. The results showed that although Pu is initially distributed on bone surfaces, it later becomes deposited throughout the bone matrix. Pu uptake by cells in resorbing areas of the periosteum, in active osteoblasts, and in chondrocytes in regions of cartilage mineralization was rapid. It concentrated more slowly on resting bone surfaces and at sites of low metabolic activity. Some unlabeled sections of skeletal tissues were immersed in a ^{241}Pu citrate solution. Autoradiography showed that Pu was bound by cell nuclei, tooth enamel matrix, dentine, predentine, and bone matrix. Binding to cartilage matrix was weak. A model is proposed to explain the distribution pattern and fate of Pu deposits in bone. (39 refs.)

77-5660 The Relative Sensitivity of Pulmonary Parenchymal Cells to ^{239}Pu Plutonium Dioxide. (Eng) Heppleston, A. G. (Univ. Dept. Pathology, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, England); Young, A. E. *Experientia* 33(10): 1346-1348; 1977.

A2G mice exposed for 10 min to a $^{239}\text{PuO}_2$ aerosol received, in separate experiments, lung doses of approx 22 or 150 nanocuries. Electron microscopy showed that the alpha particles inhaled by the mice primarily affected type II epithelial cells. The interstitial mononuclear cells, alveolar macrophages, and type I epithelium were much more resistant and appeared to react secondarily. The cellular responses, both qualitative and quantitative, exhibited a time-dose relationship. (7 refs.)

77-5661 Modification of Pulmonary Connective Tissue after Plutonium Oxide Inhalation (Meeting Abstract). (Fre) Metivier, H. (CEA, DPr/LTE, BP 561, 92542 Montrouge Cedex, France); Junqua, S.; Legendre, N.; Dewaele, J.; Masse, R.; Robert, L. *Pathol Biol (Paris)* 25(7): 474; 1977. (no refs.)

77-5662 Effect of Dose Level on Skeletal Retention of $^{239}\text{Pu(IV)}$ in the Beagle. (Eng) Stover, B. J. (Dept. Pharmacology, Univ. North Carolina, Chapel Hill NC 27514); Atherton, D. R.; Stevens, W.; Buster, D. S. Bruenger, F. W. *Radiat Res* 69(3): 442-458; 1977.

The effect of dose level on the retention of plutonium [$^{239}\text{Pu(IV)}$] in bone was examined in beagle dogs and compared to previous results on the retention of $^{239}\text{Pu(IV)}$ in the beagle liver. Each beagle received single iv injection of ^{239}Pu ranging from 0.0055 to 2.9 $\mu\text{Ci/kg}$. The animals were killed and dissected, and their bones were analyzed for ^{239}Pu . The fractional retention of ^{239}Pu in the skeleton first decreased and then approached an approx constant value. The initial fractional deposition of ^{239}Pu was independent of dose, but the long-term fractional retention was less at the lower dose level (0.0055-0.095 $\mu\text{Ci/kg}$) than at the high dose levels (0.30-2.9 $\mu\text{Ci/kg}$). The hepatic retention of ^{239}Pu , however, was found to decrease with decreasing dose level. Skeletal retention equations were developed and, together with those previously reported for the liver, used to calculate cumulative av radiation doses to the skeleton (including marrow) and to the liver throughout the lives of the beagles, which had been injected in young adulthood at six dose levels ranging from 0.016 to 2.9 $\mu\text{Ci/kg}$. The ^{239}Pu concentration in plasma was measured 1 min-12.5 yr after injection. Four exponentials were fit to the data. Samples were obtained from the dogs at six dose levels and from well, ill, and terminal dogs. The effect of dose level on the hepatic retention of ^{239}Pu was found to be opposite that on skeletal retention, because hepatic retention decreased slowly at the low and intermediate dose levels and progressively more rapidly at the three high dose levels. The cumulative radiation dose to the liver, therefore, exceeds that to the skeleton throughout the survival period for each dose level except the highest (2.9 $\mu\text{Ci/kg}$) at times > 1200 days. (18 refs.)

77-5663 Electrical Phenomena at Membrane Level (Eng.) Mehrishi, J. N. (Dept. Radiotherapeutics, Univ. Cambridge, Hills Road, Cambridge CB2 2QN, England); Loutit, J. F. *J Chim Phys* 74(5): 614-615; 1977.

Cell electrophoresis has demonstrated that T lymphocytes have a high electrophoretic mobility (HML) and B lymphocytes have a low electrophoretic mobility (LML), as

result of their surface topochemistry and resultant zeta potential. Most lymphocytes in radionuclide (^{90}Sr , ^{239}Pu)-induced leukemias were of the LML type. No HML cells were seen. The surface topochemistry of cells in leukemic mice was strikingly different from the control cells. The large decrease in the numbers of detectable phosphate and sulfhydryl groups on the leukemic cells suggested that radiation may lead to the malignant transformation of cells and an altered surface topochemistry. (3 refs.)

- 77-5664 Immunospecificity of Non-histone Chromosomal Proteins in ^{90}Sr -induced Osteogenic Sarcoma (Mouse).** (Eng.) Kono, N. (Dept. Pathology, Sch. Medicine, Kanazawa Univ. Takaramachi, Kanazawa, Ishikawa 920, Japan); Shima, I.; Ohta, G. *J Biochem* 81(5): 1549-1555; 1977.

The immunoactivity of the nonhistone chromosomal proteins (NCP) purified from an ^{90}Sr -induced osteogenic sarcoma in ddN mice was compared with that of the NCP from Ehrlich ascites tumors, normal mouse liver, and calf thymus by quantitative microcomplement fixation. Antibodies against all NCP were prepared by the immunization of albino rabbits. Antibodies against the NCP of the sarcoma showed a higher affinity for homologous antigens than did those of the Ehrlich ascites tumor, normal liver, and calf thymus. These complement-fixing antibodies reacted much more strongly with the sarcoma NCP than with those of the Ehrlich ascites tumor, and the NCP from normal mouse liver or calf thymus were virtually inactive. The results indicate that the NCP from the ^{90}Sr -induced osteogenic sarcoma are tissue-specific. (39 refs.)

- 77-5665 Dys hormonal Thyroid Tumors in Rats Following Long-Term Exposure to Radionuclides.** (Rus.) Zhorno, L. Ia. (Lab. Toxicology, Leningrad Scientific Res. Inst. Radiation Hygiene, RSFSR Ministry Public Health, Leningrad, USSR); Zapol'skaia, N. A. *Vopr Onkol* 23(8): 102-103; 1977.

Male rats received ^{45}Ca , ^{90}Sr and ^{144}Ce po (0.4-1.2 μCi) daily for 720 days. The isotopes induced thyroid and parathyroid carcinomas and thyroid adenomas. The tumor induction rates were 5/24 for ^{45}Ca , 3/22 for ^{90}Sr and 2/16 for ^{144}Ce . (6 refs.)

- 77-5666 Induction in Rats of Paranasal Sinus Carcinomas with Radioactive Cerium Chloride.** (Eng.) Jasmin, J. R. (Departement de Virologie, Institut de Cancerologie et d'Immunogenetique, Groupe Hopitalier Paul Brousse, 94800 Villejuif, France); Brocheriou,

C.; Klein, B.; Morin, M.; Smadja-Joffe, F.; Cernea, P.; Jasmin, C. *J Natl Cancer Inst* 58(2): 423-427; 1977.

Twelve male Sprague-Dawley rats received a colloidal suspension of ^{144}Ce stabilized in the form of hydroxide. The mouth was kept open so that 25 μl of a $^{144}\text{CeCl}_3$ solution could be injected in the vestibule of the left maxillary sinus, at the level of the first superior molar. The median survival of the animals was 274 days. Well-differentiated epidermoid carcinomas of the paranasal sinus were found in 8/12 rats. Three rats died before 200 days without tumor. There were no distant metastases, but lesions secondary to the radioactivity were found: bone sequestra, vascular alterations of the fibrinoid type with fibrinous thrombi, and pronounced sclerosis. (9 refs.)

- 77-5667 Histological Types of Lung Cancer in Relation to Different Conditions of Radiation Exposure.** (Cze.) Sevc, J. (Centrum hygieny zarení, Institutu hygieny a epidemiologie, Srobarova 48, 100 42 Prague 10, Czechoslovakia); Horacek, J.; Placek, V. *Cas Lek Cesk* 116(16): 503-505; 1977.

A considerably increased incidence of bronchogenic carcinoma was observed among uranium miners in Czechoslovakia. Comparison of the distribution of the various histological types of this cancer among 115 miner patients and 326 patients from the general population (control) showed that the ratios of the observed to expected incidences are 4.7 for epidermoid cancer, 6.1 for small cell carcinoma, 1.2 for adenocarcinoma, and 3.5 for other histological types among the miners. These findings refute the previous assumption that ionizing radiation induces an increased incidence of small cell bronchogenic carcinoma only. Examination of the histological types as a function of cumulative exposure to ^{222}Rn daughter products revealed that high cumulative exposure (> 400 WLM: 1 WLM = exposure to an atmosphere with a specific volumetric activity of 1.3×10^5 MeV/liter for 170 days) and high initial annual exposure were conducive to a significant increase of both the small cell and epidermoid types. Lower cumulative exposure and lower initial exposure resulted in a significant increase mainly of the small cell undifferentiated type of lung cancer. (7 refs.)

- 77-5668 The Binding of 8-Methoxypsoralen to Nuclear DNA of UVA Irradiated Human Fibroblasts In Vitro.** (Eng.) Bredberg, A. (Dept. Clinical Genetics, Karolinska sjukhuset, Stockholm, Sweden); Lambert, B.; Swanbeck, G.; Thyresson-Hok, M. *Acta Derm Venereol (Stockh)* 57(5): 389-391; 1977.

Human skin fibroblasts were exposed to ^3H -8-

methoxypsoralen (8-MOP, 3.1 and 8.1 $\mu\text{g/ml}$) and long-wave UV light in vitro. The proportions of photochemically bound 8-MOP in the nucleus and cytoplasm were studied by autoradiography. UV irradiation resulted in a significant, dose-dependent increase in the binding of 8-MOP to the cell nucleus, presumably to nuclear DNA. (12 refs.)

- 77-5669 **The Pigmentary Response to Photochemotherapy.** (Eng) Zaynoun, S. (Div. Experimental Dermatology, Dept. Dermatology I, Univ. Vienna, A-1097 Vienna, Austria); Konrad, K.; Gschnait, F.; Wolff, K. *Acta Derm Venereol (Stockh)* 57(5): 431-440; 1977.

Changes induced by systemic photochemotherapy with 8-methoxypsoralen and long-wave UV light were investigated in 11 Caucasian patients with severe generalized psoriasis. The therapy stimulated melanogenesis but did not induce significant changes in the av size of the melanosomes or their distribution patterns within keratinocytes. If cytogenetic changes are induced in melanocytes, they are not morphologically demonstrated in pigment cells or their products. (31 refs.)

- 77-5670 **Dermal Toxicity of 8-Methoxypsoralen Administered (by Gavage) to Hairless Mice Irradiated with Long-Wave Ultraviolet Light.** (Eng) Langner, A. (Dept. Dermatology, Warsaw Medical Sch., ul. Koszykowa 82a, 02-008 Warsaw, Poland); Wolska, H.; Marzulli, F. N.; Jablonska, S.; Jarzabek-Chorzelska, M.; Gliniski, W.; Pawinska, M. *J Invest Dermatol* 69(5): 451-457; 1977.

Hairless (C3H/HeH-hr) mice were given various amounts of 8-methoxypsoralen (8-MOP) by gavage prior to irradiation with longwave UV light (UVA) 2-6 times/wk for 1-12 mo. The minimum phototoxic 8-MOP dose was 20 mg/kg by this route of administration. No histologic features of cutaneous malignancy were encountered under test conditions that produced prolonged phototoxicity, deep ulceration, cicatrization, and other deformities. Repeated daily gavage doses of 20 mg/kg 8-MOP in conjunction with twice weekly UVA irradiation for 10 min elicited an erythematous phototoxic reaction, but did not give rise to subsequent skin lesions. When combined with twice weekly UVA irradiation for 10 min, daily gavage doses of 30 and 40 mg/kg 8-MOP caused severe burning with subsequent scarring, but it did not induce malignant tumors in experiments lasting 8 mo. No organ toxicity was seen except for toxic liver changes when severe cutaneous burns and pronounced ulcerations were produced. Limited immunologic studies disclosed no abnormalities in this system. (16 refs.)

- 77-5671 **Photosensitizing Effects of 8-Methoxypsoralen on the Skin of Hairless Mice--I. Formation of**

Interstrand Cross-links in Epidermal DNA. (Eng) Ley, R. D. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL 60439); Grube, D. D.; Fry, R. J. *Photochem Photobiol* 25(3): 265-268; 1977.

Two strains of genetically hairless mice (HRS/J/Anl and SKH:hr-1) received two consecutive applications of 100 μl of 8-methoxypsoralen (8-MOP) on their backs. One hour later, groups of mice were exposed to UV light at 365 nanometers (nm), 300-400 nm, or 320-400 nm. The number-av mol wt of the extracted epidermal DNA (calculated from sedimentation profiles) was approx 20×10^6 daltons for control mice and 30×10^6 daltons for mice receiving 8-MOP and 3×10^4 Joules/meter² (J/m²) of 300-400 nm UV light. This increase probably results from the photomediated induction of bifunctional psoralen adducts in the DNA. Similar results were seen in both strains with all three UV sources. In HRA/J/Anl mice treated with 300-400, 320-400, and 365 nm, the relative efficiencies for 8-MOP-UV-induced DNA cross-linkages (m²/J/dalton $\times 10^{-13}$) were 3.5, 2.5, and 0.7, respectively; the corresponding values in SKH:hr-1 mice were 3.5, 2.3, and 0.7. Additional cross-linking efficiencies were determined for mice subjected to multiple treatments five times per week for 6 wk. They were 2.4 and 0.4 for HRS/J/Anl mice treated with 300-400 and 365 nm and 2.3 and 0.4 for SKH:hr-1 mice. This reduction of approx 33% in cross-linkages could result from a decreased penetration of 8-MOP to the basal layer and/or a decreased transmission of UV. The relationship of these findings to tumorigenesis is discussed. (14 refs.)

- 77-5672 **Sister Chromatid Exchanges in Photochemotherapy.** (Eng.) Wolff-Schreiner, E. C. (Dept. Dermatology, Univ. Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria); Carter, D. M.; Schwarzacher, H. G.; Wolff, K. *J Invest Dermatol* 69(4): 387-391; 1977.

Although 8-methoxypsoralen and long-wavelength UV light photochemotherapy of human peripheral lymphocytes in vitro results in an increase in the observed number of sister chromatid exchanges, this same combination in a clinical trial on 19 patients produced no exchanges. Studies for up to 26 mo failed to demonstrate a cumulative effect. These findings do not exclude the possibility of harmful effects on other tissues. (29 refs.)

- 77-5673 **Repair of DNA Damage Induced by Ionizing Radiation and Benzo(a)pyrene in Mammalian Cells.** (Eng.) Cerutti, P. A. (Dept. Biochemistry and Molecular Biology, J. Hillis Miller Health Center, Box J-245, Univ. Florida, Gainesville, FL 32610); Shinohara, K.; Remsen, J. *J Toxicol Environ Health* 2: 1375-1386; 1977.

Studies of the excision of γ -ray products of the 5,6-

hydroxydihydrothymine (DHT)-type from the DNA of fibroblasts from normal human subjects and from patients with the hereditary diseases Fanconi's anemia (FA) and ataxia telangiectasia (AT) are reviewed. Two FA strains (FA CCL 2 and FA 1802B) displayed a decreased capacity for the removal of DHT from γ -irradiated DNA, suggesting that FA is a "DNA repair disease." Four AT strains (AT CRL 1312, AT CRL 1343, AT GM 367, and AT 4 B1) possessed normal DHT excision capacity. Studies of the formation and repair of DNA-benzo(a)pyrene (BP) adducts in baby hamster kidney cells (BHK 21/C13), secondary mouse embryo fibroblasts [MEF (C57BL)], and human lymphoma cells (HR-B Ramos) are also reviewed. The formation of DNA-BP adducts was seen only in the rodent lines: BHK cells removed about 28% of the adducts from DNA within 24-hr, but MEF cells removed only 15% within the same period. (37 refs.)

77-5674 Induction and Persistence of Pyrimidine Dimers in the Epidermal DNA of Two Strains of Hairless Mice. (Eng.) Ley, R. D. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL 60439); Sedita, A.; Grube, D. D.; Fry, R. J. *Cancer Res* 37(9): 3243-3248; 1977.

Observations in mice of strain-dependent differences in susceptibility to photocarcinogenesis led to an investigation of a possible strain difference in the capacity of mouse epidermal cells to excise UV-induced damage from the DNA. UV is known to cause the formation of pyrimidine dimers in DNA. These dimers are recognized by damage-specific endonucleases from *Micrococcus luteus*, which were used to assay the induction and fate of UV-induced sensitive sites (ESS) in the DNA of mouse epithelial cells *in vivo* for two strains of hairless albino mice. Velocity sedimentation profiles from alkaline sucrose gradients of DNA extracted from epithelial cells of mice previously exposed to radiation from an FS40 lamp (280 to 400 nanometers) and exposed to *M. luteus* endonucleases revealed the presence of randomly distributed ESS. The rates of induction of ESS in the DNA of HRS/J and SKH:hr-1 mice were $6.1 \pm 0.5 \times 10^{-11}$ and $6.5 \pm 0.8 \times 10^{-11}$ ESS/dalton/joule/m², respectively. At 24 hr after radiation, these values were $6.5 \pm 0.8 \times 10^{-11}$ and $5.2 \pm 1.3 \times 10^{-11}$ ESS/dalton/joule/m² respectively, indicating little or no repair. Approx 80% of the ESS were cyclobutyl pyrimidine dimers, according to enzymatic photoreactivation with a fast photoreactivating enzyme. The data show that, *in vivo*, mouse epithelial cells have little or no capacity for the excision repair of pyrimidine dimers. (26 refs.)

77-5675 DNA Repair in Arrested Human Diploid Fibroblast Cultures Irradiated with Ultraviolet Light (Meeting Abstract). (Eng.) Kantor, G. J. (Dept. Bio-

logical Sciences, Wright State Univ., Dayton, OH 45431); Hull, D. R. *Biophys J* 17(2): 144a; 1977. (no refs.)

77-5676 Acridine Probe Study into Synergistic DNA-Denaturing Action of Heat and Ultraviolet Light in Squamous Cells. (Eng) Roth, D. (Inst. Dental Res., New York Univ. Dental Center, 339 E. 25th St., New York, NY 10010); London, M. *J Invest Dermatol* 69(4): 368-372; 1977.

Acriflavine was used as fluorescent probe to distinguish between native and denatured DNA in a study of the synergistic DNA-denaturing action of heat on UV light in human squamous cells. The acriflavine intercalates into DNA at 4 C and its fluorescence is quenched, but when the temperature is raised to 25 C, the relatively unstable DNA-acriflavine bonds at single-stranded sites dissociate, but those at double-stranded sites do not. Thermal dissociation of intercalative complexes between acriflavine and purified calf thymus native DNA begins at approx 35 C, but with UV-irradiated DNA, dissociation occurs from 0 C and up, indicating UV-induced denaturation. Parallel results were found with squamous cell DNA. Cells were irradiated at various temperatures (24, 32, or 42C), and the denaturation rate increased with increasing temperature. The highest of the three (42 C) is the temperature to which human skin (antecubital) is raised after 15 min exposure to the sun on a clear, windless day at 26° north latitude. It was suggested that heating of the skin surface by the sun may add substantially to the DNA-denaturing action of UV on human squamous cells and, perhaps, predispose them to carcinogenic consequence. (22 refs.)

77-5677 Effect of Transient Lambda Prophage Induction on Ultraviolet Light Resistance and Recombination in Escherichia coli. (Eng.) Braun, A. (Dept. Radiation Therapy, Harvard Medical Sch., Boston, MA 02115); Gluck, D. *J Bacteriol* 131(1): 208-213; 1977.

It was recently found that a recombination system coded for by bacteriophage λ , the *red* system, can enhance the x-ray survival of some Rec- *Escherichia coli* mutants, presumably by increasing the recombination proficiency of these cells. These results were extended here to the UV response of transiently induced Rec- lysogens. In addition, the effect of transient prophage induction on genetic recombination in Hfr x F- (Rec-) matings was investigated. Transient induction of λ prophage increased the UV resistance of most exponentially growing *E. coli* lysogens. Resistance was increased in wild-type, *recB*, *recB recC*, *recB recC recF*, and *recB recC recL* hosts. No enhancement in *recA* lysogens was found, nor was there enhancement in stationary cultures. Transient induction also increased the genetic recombination rate in *recB* lysogens, as measured in Hfr x F- crosses. In both cases, a *red*-dependent enhancement was observed. (23 refs.)

- 77-5678 **Influence of Wind on Chronic Ultraviolet Light-induced Carcinogenesis.** (Eng) Owens, D. W. (Section Dermatology, Kelsey Seybold Clinic, Houston, TX 77030); Knox, J. M.; Hudson, H. T.; Rudolph, A. H.; Troll, D. *Br J Dermatol* 97(3): 285-287; 1977.

Wind enhances the carcinogenic effect of chronic UV radiation. This was demonstrated in hairless mice that were irradiated for 42 wk with mercury arc lamps. One group of animals was exposed to a continuous wind flow 2.7 meter/sec except for the 1-2 min/day when they were irradiated. Another group of animals received identical irradiation but were protected from the wind. The first tumor appeared in the UV and wind group after 105 days of irradiation, and at 164 days all surviving mice had developed tumors. In mice receiving identical irradiation but protected from the wind, the first tumor appeared at 154 days of irradiation, and by 164 days only 40% of the mice had developed tumors. (5 refs.)

- 77-5679 **Mutagenic and Epigenetic Influence of Caffeine on the Frequencies of UV-induced Ouabain-resistant Chinese Hamster Cells.** (Eng) Chang, C. C. (Dept. Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI 48824); Philipps, C.; Trosko, J. E.; Hart, R. W. *Mutat Res* 45(1): 125-136; 1977.

Caffeine (0.9 milliM), when added to UV-irradiated Chinese hamster cells, modified the frequency of induced mutations at the ouabain resistance locus. The mutation frequencies increased when caffeine was added during the period of DNA repair and mutation fixation. When caffeine was added after this period, or immediately after DNA damage and for the entire repair and selection period, mutation frequencies were reduced. It is hypothesized that caffeine, by blocking constitutive error-free postreplication repair, allows an error-prone DNA repair to produce many mutations. Moreover, caffeine, possibly by modifying cyclic AMP metabolism represses induced mutations, which, in effect, explains its antimutagenic and anticarcinogenic properties. (64 refs.)

- 77-5680 **A Quantitative Assay of Mutation Induction at the Hypoxanthine-Guanine Phosphoribosyl Transferase Locus in Chinese Hamster Ovary Cells (CHO/HGPRT System): Development and Definition of the System.** (Eng) O'Neill, J. P. (Univ. Tennessee-Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN 37830); Brimer, P. A.; Machanoff, R.; Hirsch, G. P.; Hsie, A. W. *Mutat Res* 45(1): 91-101; 1977.

Utilizing 6-thioguanine resistance, an assay was developed to measure mutation induction at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in Chinese hamster ovary K₁-BH₄ cells. After treatment with physical or

chemical mutagens, more than 98% of the isolated clones had altered HGPRTase activity, indicating the specificity necessary for a gene locus mutational assay. (18 refs.)

- 77-5681 **A Quantitative Assay of Mutation Induction at the Hypoxanthine-Guanine Phosphoribosyl Transferase Locus in Chinese Hamster Ovary Cells (CHO/HGPRT System): Utilization with a Variety of Mutagenic Agents.** (Eng) O'Neill, J. P. (Univ. Tennessee-Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN 37830); Couch, D. B.; Machanoff, R.; San Sebastian, J. R.; Brimer, P. A.; Hsie, A. W. *Mutat Res* 45(1): 103-109; 1977.

The hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in Chinese hamster ovary K₁-BH₄ cells was used to measure induction of mutations by a variety of mutagens. Among those tested were UV light, x-rays, ICR-191, ethyl methanesulfonate, N-methyl-N'-nitro-N-nitrosoguanidine, *cis*-dichlorodiamine platinum (II) and the promutagen dimethylnitrosamine. This system is a valuable tool for the study of mutagenesis in mammalian cells. (11 refs.)

- 77-5682 **A Study of Time Trends in Maternal-Fetal X-ray Exposure.** (Eng) Dales, L. G. (Dept. Medical Methods Res., Permanente Medical Group, 3700 Broadway, Oakland, CA 94611); Ury, H. K.; Friedman, G. D.; Eads, W. *Am J Epidemiol* 106(5): 362-369; 1977.

A reduction in childhood leukemia incidence in one county prompted a survey of changes in maternal-fetal x-ray exposure. Among white and black women without major obstetrical complications, there was a small but significant decline in use of abdominal-pelvic region x-rays over time (1947 to 1973); the total sample showed no significant change. Women with complications had a non-significant increase in x-ray exposure over time. It is probable that changes in hospital equipment have substantially reduced the amount of radiation delivered. (12 refs.)

- 77-5683 **Age Variation in the Cancer Risks from Foetal Irradiation.** (Eng) Kneale, G. W. (Dept. Social Medicine, Univ. Birmingham, Edgbaston, Birmingham, England); Stewart, A. M. *Br J Cancer* 35(4): 501-510; 1977.

A modified Mantel-Haenszel analysis of the data in the Oxford Survey of Childhood Cancers was used to study the age variation in cancer risks from fetal irradiation. For reticulo-endothelial system (RES) neoplasms and lymphatic leukemia, the ratio of observed to expected cases was highest between the ages of 4 and 9 yr. An analysis of other RES

neoplasms indicated a bimodal incidence of excess observed/expected cases: between birth and 1 yr and again between 4 and 7 yr. For solid tumors, the ratio was higher than expected between birth and 3 yr, and between ages 6 and 15 yr. Wilms' tumor and neuroblastomas had a higher incidence than expected between birth and 3 yr and between 6 and 9 yr. Other solid tumors had higher incidences than expected between ages 6 and 9 yr. These studies indicate that fetal irradiation accounted for a higher proportion of deaths between the ages of 5 and 10 than of deaths at earlier or later ages. This finding is compatible with later origins for radiogenic tumors than idiopathic ones which prove fatal before the age of 10. (17 refs.)

77-5684 Enhancement of X-Ray-induced Transformation in C3H/10T1/2 Cells by Interferon. (Eng.) Brouty-Boye, D. (I.R.S.C., Lab. Viral Oncology, 7, rue Guy Mocquet, 94800 Villejuif, France); Little, J. B. *Cancer Res* 37(8, part 1): 2714-2716; 1977.

The influence of interferon (IF) on x-ray transformation in vitro was studied in 10T1/2 mouse embryo fibroblast cells. Mouse IF was added to exponentially growing cells 24 hr prior to irradiation with 400 rads at a concentration of 200 units/ml. The cultures were maintained for 6-7 wk, and the dense colonies of transformed cells (type III foci) that developed were scored. Upon injection into syngeneic hosts, 80%-100% of type III foci induced by x-rays led to large nonregressing tumors. Fresh IF was included in each medium change during the incubation period. The transformation frequency following irradiation alone was 0.01%-0.06%. When the cells were continuously maintained in the presence of IF, the transformation frequency was 0.7%-2.9%. Because of the growth-inhibitory effect produced by the continuous presence of IF, the colonies of IF-treated cells were smaller and less dense than those of nontreated cells. On the basis of these results it is suggested that the effect of IF on x-ray transformation is related to its suppressive effect on cell division during the proliferative phase of the expression of transformational damage. (12 refs.)

77-5685 Can Radiation Induce Interstitial-Cell (Leydig-Cell) Tumours of the Testis? (Eng.) Hulse, E. V. (Medical Res. Council, Radiobiology Univ, Harwell, Didcot, Oxon OX11 ORD, England). *Int J Radiat Biol* 32(2): 185-190; 1977.

The testes of 3-mo-old albino rats were x-irradiated: either both testes were irradiated through the ventral wall of the scrotum, or the left testis was pushed into the abdomen and shielded and only the right testis was irradiated. The dose ranged from 100 to 1,500 R. All resulting tumors were interstitial cell tumors. However, there was no statistically significant evidence that irradiation played any part in the produc-

tion of the testicular tumors. The incidence was not statistically different whether the exposure was bilateral (13 tumors/120 rats) or unilateral (4/119), and it did not differ significantly between irradiated and nonirradiated testes (1/30). There was also no variation with the amount of radiation exposure, based on combined data for bilaterally and unilaterally irradiated testes. It is concluded that testicular tumors need not be regarded as an important hazard to persons receiving radiation. (17 refs.)

77-5686 Response of Normal and 1000-R Localized Thyroid X-Irradiated Dogs to Acute Cold Exposure. (Eng) Quinlan, W. J. (Univ. Rochester Sch. Medicine, Rochester, NY); Michaelson, S. In: *Radiation-Associated Thyroid Carcinoma*. Degroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): pp. 213-214; 1977.

Adult dogs exposed 8 to 9 yr previously to 1,000 R localized thyroid x-irradiation and normal dogs were placed in a 4°C room for 6 hr. Three of four irradiated dogs had two peaks in thyroid stimulating hormone levels during cold exposure. There was no response in the other dog. Only one of five normal dogs had two peaks; the other four had one peak. Other data on cold exposure of dogs following head and neck irradiation are outlined. (no refs.)

77-5687 Results of Screening Patients with Prior Irradiation to the Head and Neck in Five Detroit Area Hospitals. (Eng) DiGuilio, W. (William Beaumont Hosp., Detroit, MI); Douglas, R.; Fink-Bennett, D.; Levine, A.; Miller, J. M. In: *Radiation-Associated Thyroid Carcinoma*. Degroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): pp. 33-34; 1977.

Screening results on 857 patients with a history of head and neck irradiation are reported. Of 55 (6.5%) who have undergone surgery, 12 (1.5%) had differentiated thyroid carcinomas. Normal thyroids were seen in 73% of patients, and most of the abnormalities seen were minor. (no refs.)

77-5688 Thyroid Neoplasms in a Population Irradiated for Scalp Tinea in Childhood. (Eng) Modan, B. (Dept. Clinical Epidemiology, Chaim Sheba Medical Center, Tel Hashomer, Israel); Ron, E.; Werner, A. In: *Radiation-associated Thyroid Carcinoma*. Degroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): 539 pp.; 449-457; 1977.

The incidence of thyroid neoplasms was investigated in 10,842 children who received 350 to 400 rads to each

of five areas of the head on 5 consecutive days, in an equal number of controls, and in 5,400 sibling controls. The irradiated group had tumors of the brain (8, 2/8 probable), parotid (4), bone (2), thyroid (12), and scalp (1) plus leukemia (7), lymphoma (8), and various other tumors (7). The controls had tumors of the brain (1 probable), bone (1), thyroid (2), and head (2) plus leukemia (5), lymphoma (5), and various other tumors (5). In the sibling group, there were brain (1) and thyroid (1) tumors, leukemias (2), lymphomas (5), and other tumors (2). There was a significant increased risk of malignant and benign tumors in the irradiated group as compared to both control groups. The most striking excess risk for malignant tumors was seen in the brain, parotid and thyroid. There was a dose response effect for all head and neck tumors, but not for other neoplasms. The 12 thyroid cancers (9 women, 3 men) reflected a 6-fold increase as compared to controls. All patients had been irradiated between ages 2 and 10 yr; 10 had received a single treatment only. The latent period ranged from 4 to 21 yr. These findings emphasize the need for continued surveillance of children who have received head and neck irradiation. (11 refs.)

- 77-5689 **Breast Carcinoma Following Radiotherapy of Metastatic Wilms' Tumor.** (Eng) Reimer, R. R. (Room A521, Landow Building, Environmental Epidemiology Branch, NCI, Bethesda, MD 20014); Fraumeni, J. F.; Reddick, R.; Moorhead, E. L. *Cancer* 40(4): 1450-1452; 1977.

A 22-yr-old woman developed breast cancer 15 yr after radiotherapy to the lung for a metastatic Wilms' tumor. Her mother had died of bilateral breast cancer at age 32, which suggests a genetic predisposition to radiogenic cancer. Recent improvements in the survival of children with certain cancers necessitate long-term surveillance for iatrogenic neoplasia, particularly when familial susceptibility is evident. (21 refs.)

- 77-5690 **Renal Carcinoma 30 Years after Abdominal Irradiation for Testicular Seminoma (Letter to Editor).** (Eng.) Khandekar, J. D. (Div. Medical Oncology, Evanston Hosp., Evanston, IL); Neulist, L.; Dotson, L. *Lancet* 2(8038): 615; 1977.

The case is presented of a 75-yr-old man who developed renal carcinoma 30 yr after that side of his body had been irradiated for testicular seminoma. The radiation dose had totaled 3,000 rads. Since renal biopsy was not performed, it is not known whether there was associated radiation nephritis. (4 refs.)

- 77-5691 **Delayed Sequelae of Occupational Irradiation of Different Intensity (Pathogenetic Me-**

chanisms). (Rus.) Gus'kova, A. K. (Scientific Res. Inst. Industrial Hygiene and Occupational Diseases, Acad. Medical Sciences USSR, Moscow, USSR); Soldatova, V. A.; Denisova, E. A.; Gribova, I. A.; Gorbarenko, N. I.; Kirsanova, G. I.; L'vovskaia, E. N. *Med Radiol (Mosk)* 22(5): 49-54; 1977.

The results of a long-term follow-up examination of 2,873 persons who had occupational exposure to ionizing radiation are presented. The subjects were divided into two groups. Group 1 included 1,575 persons whose total irradiation dose did not exceed 30-100 rads. From 5.9% to 18%-21% showed regional hypotension, 8.6%-17.2% had bradycardia, and 16.2%-27.2% had electrocardiographic disturbances. Group 2 included 1,298 persons who were exposed to doses that exceeded the max tolerance dose (> 150 rads). Atherosclerotic changes of the cerebral vessels were observed in 49% (compared to 32% of controls), the frequency of hypercholesterolemia in subjects > 40 yr was 57.9% (compared to 25.7% in controls), and mild leukopenia (4,000-4,900 cells/ μ l) was detected in 41% of the patients. (19 refs.)

- 77-5692 **Capillary Microscopic Observation on the Superficial Minute Vessels of Atomic Bomb Survivors, Hiroshima, 1972-73.** (Eng) Tsuya, A. (Dept. Radiology, Cancer Res. Inst. Hosp., Tokyo, Japan); Wakano, Y.; Otake, M.; Dock, D. S. *Radiat Res* 72(2): 353-363; 1977.

Capillary morphology was studied during 1972-73 in 1,374 atomic bomb survivors (567 men and 807 women) and correlated to radiation dose; the results were compared to a similar study conducted in 1956-57. A significant late somatic effect of radiation at the fingernail fold was demonstrated in those who were under 10 yr of age at the time of the bomb and were exposed to ≥ 100 rads. The effects observed by studying the labial or lingual mucosa were not statistically significant, as compared to significant effects seen in the previous study. However, a greater frequency of abnormalities was still noted at these sites in patients exposed to ≥ 100 rads and under 10 yr old at the time of the bomb. Thus it appears that radiation-induced capillary damage has persisted with minimal repair. No significant difference in aging was detected between control and exposed populations, suggesting that the life-shortening effects of radiation are related instead to the increased risk of cancer. (16 refs.)

- 77-5693 **Stomach Cancer in Atomic-Bomb Survivors (Letter to Editor).** (Eng) Nakamura, K. (Natl. Inst. Industrial Health, Ministry Labour, Nagao, Tama-ku, Kawasaki, Japan). *Lancet* 2(8043): 866-867; 1977.

For Hiroshima atomic bomb survivors, the standardized mortality ratio for stomach cancer rose steadily with increasing dose, but a statistically significant increase was observed

only in the highest dose group (≥ 200 rads). For Nagasaki survivors, this dose-dependence was not observed; however, an excess of stomach cancer mortality occurred at ≥ 500 rads. The Hiroshima data suggest a role for irradiation. Since neutrons made up more of the radiation in Hiroshima and the relative biological effectiveness of neutrons relative to γ radiation is > 1 , the radiation effect in Nagasaki may be weaker for a fixed-dose level. (4 refs.)

77-5694 Breast Cancer Incidence among Atomic Bomb Survivors, Hiroshima and Nagasaki, 1950-69. (Eng.) McGregor, D. H. (Veterans Admin. Center, 4801 Linwood Blvd., Kansas City, MO 64128); Land, C. E.; Choi, K.; Tokuoka, S.; Liu, P. I.; Wakabayashi, T.; Beebe, G. W. *J Natl Cancer Inst* 59(3): 799-811; 1977.

During the period 1950-1961, 787 cases of breast cancer among female atom bomb survivors and 54 among nonirradiated controls were identified. The estimated absolute risk over this period for women ≥ 10 yr of age at the time of bombing (ATB) was 1.9 excess cases/ 10^6 person-years/rad. This value is substantially lower than published estimates based on x-ray and fluoroscopy data from smaller samples of younger North American women. The Hiroshima and Nagasaki dose-response curves were similar, suggesting approx carcinogenic equivalence of neutron and γ radiations, and they were consistent with a linear model. For women of comparable ages ATB, there was little evidence of dose-dependence in the latent period or that exposure caused cancer at an earlier age than usual. No breast cancers were seen in survivors < 10 yr old ATB, and prior to 1960, no substantial number of cases was reported in those who were 10-19 yr old ATB. By 1965-1969, however, there was a much greater excess of breast cancer in women who were 10-19 yr old ATB and who were exposed to medium or high doses than among women who were ≥ 35 yr old ATB and exposed to any dose level. This suggests that the breast tissues of adolescent females may be more sensitive to the effects of ionizing radiation than those of older women. By 1969, the expected lifetime incidence of breast cancer had been approximated or exceeded in all age-ATB groups. (40 refs.)

77-5695 Neutron Doses to Patients in High Energy X-ray Therapy. (Eng.) Stranden, E. (State Inst. Radiation Hygiene, Osterndalen 25, 1345 Osteras, Norway). *Phys Med Biol* 22(5): 1011-1013; 1977.

The neutron fluxes and energy distribution resulting from high energy x-irradiation of patients was calculated. The study indicated that the dose equivalents to the eye, gonad, and ovary resulting from a 200 rad exposure of a 10×10 cm thoracic field were 0.4, 0.4, and 0.2 rem, respectively. (7 refs.)

77-5696 Microdosimetry and Chromosome Aberrations: Effects of 230 KeV Neutrons on *Vicia faba* Chromosomes. (Eng) Geard, C. R. (Radiological Res. Lab., Dept. Radiology Columbia Univ., Coll. Physicians and Surgeons, New York, NY 10032). *Mutat Res* 44(3): 345-358; 1977.

The radiobiologic effects of ionizing radiation were investigated by relating physical energy deposition events to subnuclear cytological events (chromosomal changes) in metaphases of *Vicia faba* cells. The 230-kiloelectron volt (KeV) neutrons produced about 0.4 recoil proton per late interphase nucleus per rad, with most protons traveling 1 to 2 microns (μm) from their origin, depositing energy at about 90 KeV/ μm . The frequency of induced aberrations was linear with dose. Distributions of chromosomal aberrations and total cytological events indicate that some proton recoils produce multiple events. It was found that the highly energetic recoil protons (approx 90 KeV/ μm) can induce multiple events and are therefore the ones most likely to produce effects that result in cell death. (11 refs.)

77-5697 Alpha-particle-induced Transformation in a C3H Mouse-Embryo-derived Cell Line (Meeting Abstract). (Eng) Lloyd, E. L. (Argonne Natl. Lab., Argonne, IL 60439); Gemmell, A.; Henning, C. B.; Gemmell, D. S.; Zabransky, B. J. *In Vitro* 13(3): 181; 1977. (no refs.)

See also:

*(Rev.): 77-5418, 77-5419, 77-5420, 77-5421, 77-5432, 77-5433, 77-5434, 77-5435, 77-5445.

*(Chem.): 77-5571, 77-5644, 77-5645, 77-5646.

*(Viral): 77-5735, 77-5736, 77-5737, 77-5738, 77-5764.

*(Immun.): 77-5856, 77-5872, 77-5942.

*(Epid.-Biom.): 77-5957.

VIRAL CARCINOGENESIS

- 77-5698 **Morphological and Histochemical Properties of Human Embryonic Cells Transformed by Rous and Polyoma Viruses.** (Eng) Shevliaghyn, V. J. (Gamaleya Inst. Epidemiology and Microbiology, Acad. Medical Sciences, Moscow, USSR); Karzas, N. V.; Amchenkova, A. M. *Neoplasma* 24(4): 375-385; 1977.

Human embryonic cells transformed by Rous sarcoma virus (stable cell line 23) or by polyoma virus (stable cell line P-2) differ morphologically from normal human embryonic cells. The mitotic activity of P-2 and 23 cells was 51 and 48/1000, respectively, compared with 28/1000 for normal human embryo fibroblasts. The duration of cell cycle generation time was 20 hr for P-2 cells, 18 hr for 23 cells, and 18 hr for normal cells. The G₁ period lasted 6 hr in both transformed cell lines; the S period of the P-2 and 23 cells was 8 and 6 hr, respectively. Both cell lines had high content of RNA, DNA, and protein-bound SH groups and had a high activity of acid phosphatase, acid RNase, and glucose-6-phosphatase. The transformed cells did not differ from normal cells in glycogen content, distribution of acidic mucopolysaccharides, or NADPH-tetrazolium reductase and succinic dehydrogenase activities. (23 refs.)

- 77-5699 **Presence of DNA Polymerase in Lymphosarcoma in Northern Pike (*Esox lucius*).** (Eng.) Papas, T. S. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD 20014); Pry, T. W.; Schafer, M. P.; Sonstegard, R. A. *Cancer Res* 37(9): 3214-3217; 1977.

Northern pike lymphosarcoma DNA polymerase was partially purified from particulate fractions banding at 1.15-1.16 g/ml from homogenates prepared from frozen necropsies of tumor-bearing pike. Many of its properties are similar to known retrovirus DNA polymerases, especially that of avian myeloblastosis virus (AMV). The template primer preference of the polymerase is for ribotemplates, like a typical reverse transcriptase. Its isoelectric point is 5.5, and it is eluted from phosphocellulose with 0.22 M potassium phosphate. The pike lymphosarcoma polymerase is inhibited by pyran, a specific inhibitor of viral polymerases. The optimum temperature (T_m) profile of this enzyme is, however, remarkably different from those reported for other polymerases. At 5 C the enzyme exhibits 82% of its optimum activity, with a T_m of 20 C; only 35% of its activity is retained at 35 C. The mammalian virus DNA polymerase of Rauscher leukemia virus has a T_m of 30 C, and two avian viral enzymes (from AMV and Rous sarcoma virus) have a T_m of 38 C. It is suggested that this thermal lability may restrict the presumptive pike lym-

phoma virus to poikilotherms and prevent its infection of homeotherms. There is a marked seasonal periodicity of epizootics of pike lymphoma, with tumors developing during the cold water periods and spontaneously regressing during the warm water periods. (18 refs.)

- 77-5700 **Extensive In Vitro Transcription of Rous Sarcoma Virus RNA by Avian Myeloblastosis Virus DNA Polymerase and Concurrent Activation of the Associated RNase H.** (Eng) Darlix, J. L. (Departement de Biologie Molculaire, Universite de Geneve, CH-1211 Geneva 4, Switzerland); Bromely, P. A.; Spahr, P. F. *J Virol* 23(3): 659-668; 1977.

To measure the influence of various parameters on the reverse transcription of Rous sarcoma virus (RSV) 70S RNA by avian myeloblastosis virus (AMV) DNA polymerase in vitro, in situ analysis of the RNA sequences transcribed and DNA-RNA annealing studies were conducted. Optimal transcription (55%-60% of the RSV RNA template after 1 hr) occurred when incubation was carried out at 44 C using 5 milliM MgCl₂, 80 milliM NaCl, and 0.5-1.0 milliM MnCl₂. Analysis of RNA sequences transcribed after 5 min reaction showed that > 75% of all RNA molecules were transcribed at the 5' terminus and at two other sites near the center of the subunit RNA. Synthesized RSV DNA was essentially single-stranded, had a chain length ranging from a few hundred to 5,200 nucleotides (half of it being > 1,000 residues), and after hybridization with excess RNA, could protect all RSV RNA sequences against RNase digestion. The last characteristic was determined by quantitation of all large RSV oligonucleotides. Activation of the RNase H associated with AMV DNA polymerase in vitro was observed. (26 refs.)

- 77-5701 **Phenotypic Mixing Between Reticuloendotheliosis Virus and Avian Sarcoma Viruses.** (Eng.) Vogt, P. K. (Dept. Microbiology, Univ. Southern California Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA 90033); Spencer, J. L.; Okazaki, W.; Witter, R. L.; Crittenden, L. B. *Virology* 80(1): 127-135; 1977.

Because there is evidence that unrelatedness is no obstacle to phenotypic mixing, the interaction between reticuloendotheliosis virus (REV) and avian sarcoma virus (ASV) was investigated. Type C/O chick embryo fibroblasts (CEF) were coinfecting with RSV(RAV-O) [Bryan high-titer strain Rous

sarcoma virus (Rous-associated virus), multiplicity of infection (MOI), 10^{-3} focus-forming units (FFU)/cell] and REV (MOI 10^{-1} fluorescent FFU/cell). After 7 days, harvests were taken and assayed on type C/E chicken cells. Coinfection led to the formation of ASV pseudotypes that carried envelope determinants of REV. These pseudotypes could be neutralized by REV antiserum, had a host range that was different from that of any known ASV, and were susceptible to specific viral interference by REV. Although the results do not rule out the possibility that some other virus was present in REV stocks (which were plaque-purified), the probability for an unrecognized contaminant was considered remote. The REV stocks were free of avian leukosis virus according to the CO-FAL test, and their ability to form pseudotypes with ASV was neutralized with specific REV antiserum. (44 refs.)

77-5702 Reduced Levels of Adenosine Deaminase in Chick Embryo Fibroblasts Transformed by Rous Sarcoma Virus. (Eng) Chiang, P. K. (Lab. General and Comparative Biochemistry, Natl. Inst. Mental Health, Bethesda, MD 20014); Cantoni, G. L.; Ray, D. A.; Bader, J. P. *Biochem Biophys Res Commun* 78(1): 336-342; 1977.

Adenosine deaminase activity in chick embryo fibroblasts was substantially decreased after transformation by the Bryan high-titer strain (RSV-BH) or the Schmidt-Ruppin strain (RSV-SR) of Rous sarcoma virus. Concomitant with this reduction in enzyme activity, there was an increased uptake of exogenous adenosine into all of the RNA species from virus infected cells. This increase could be attributed to reduced degradation of adenosine as a result of the decreased level of adenosine deaminase, an alteration in the rate of uptake of adenosine, or a change in the intracellular phosphorylation capacity of adenosine. Levels of adenosine deaminase in the lymphocytes from chronic lymphocytic leukemia patients are consistently lower than those in lymphocytes from normal subjects. The effect that reduced levels of this enzyme has on other metabolic parameters in RSV-transformed cells remains to be clarified. (21 refs.)

77-5703 Integration of Proviral DNA in Chicken Cells Infected with Schmidt-Ruppin Rous Sarcoma Virus Is Not Enhanced by DNA Repair. (Eng) Tsuruo, T. (Dept. Pathology, UCLA Sch. Medicine, Los Angeles, CA 90024); Baluda, M. A. *J Virol* 23(3): 533-542; 1977.

DNA repair was induced in normal chick embryo fibroblast (CEF) monolayers by treatment with UV light or 0.5 $\mu\text{g}/\text{ml}$ 4-nitroquinoline 1-oxide at intervals ranging from 6 hr before to 24 hr after infection with Schmidt-Ruppin strain A of Rous sarcoma virus (SR-RSV-A). To allow for max integration of the exogenous provirus and for elimination of free

proviral DNA, CEF were subsequently cultured for 18 to 20 days and harvested, and the DNA was extracted. Filter hybridization of excess ^3H -labeled 35S SR-RSV-A RNA to cellular DNA indicated that the DNA repair induced did not affect the concentration of proviral DNA present per infected cell. Results of liquid hybridization experiments using an excess of DNA correlated with these results. Both methods showed that only one or two exogenous proviruses are integrated per haploid cell genome. Proviral integration appears to be restricted to specific sites, and a specific enzymatic recombination mechanism may be involved in the reaction. (56 refs.)

77-5704 Transforming Action of Total RNA Preparations Isolated from Rous Virus-induced Sarcomas. (Rus.) Zhudina, A. I. (Lab. Mechanisms Carcinogenesis, N. N. Petrov Scientific Res. Inst. Oncology, Leningrad, USSR); Pluzhnikova, G. F.; Lindeberg, T. Ia. *Vopr Onkol* 23(7): 26-34; 1977.

The transforming effect of total RNA preparations isolated from Rous virus (RV) producing chick sarcomas and from hamster sarcomas not producing RV on chick and hamster embryonal cell cultures was studied. The tumors had been induced by the same strain (Carr-Zilber) of RV in both species. Both RNA preparations caused morphological transformation and proliferation of the chick and hamster embryo cells starting from the fifth to the ninth day. The RNA preparations from the hamster sarcoma not producing RV were even more active in terms of cell transformation and proliferation than preparations from the virus-producing chick sarcoma. Hamster embryonal cells were more sensitive to the transforming effect of total RNA preparations than the chick embryo cells. Although DNase had hardly any effect on the activity of the total RNA preparations, RNase reduced it considerably but not completely. (6 refs.)

77-5705 Size and Genetic Content of Viral RNAs in Avian Oncovirus-infected Cells. (Eng) Hayward, W. S. (Rockefeller Univ., New York, NY 10021). *J Virol* 24(1): 47-63; 1977.

Viral complementary DNA (cDNA) sequences corresponding to the *gag*, *pol*, *env*, *src*, and *c* regions of the Rous sarcoma virus (RSV) genome were selected by (1) hybridizing viral cDNA to RNA from viruses that lack the *env* or *src* gene or to polyadenylic acid [poly(A)]-containing RNA fragments of different lengths and (2) isolating either hybridized or unhybridized DNA. The specificities, genetic complexities, and map locations of the selected cDNA's agreed with the size and map locations of the corresponding viral genes. Analyses of virus-specific RNA, using the specific cDNA's as molecular probes, demonstrated that oncovirus-infected cells con-

tained genome-length (30-40S) RNA plus one or two species of subgenome-length viral RNA. The size and genetic content of these RNA's varied, depending on the genetic makeup of the infecting virus, but in each case the smaller RNA's contained only sequences located near the 3' end of the viral genome. Three RNA species were detected in Schmidt-Ruppin RSV-infected cells: 39S (genome-length) RNA; 28S RNA, with an apparent sequence of *env-src*-cpoly(A); and 21S RNA, with an apparent sequence of *src-c*-poly(A). Cells infected with the Bryan high-titer strain RSV, which lacks the *env* gene, contained genome-length (35S) RNA and 21S *src*-specific RNA, but not the 28S RNA species. Leukosis virus-infected cells contained two detectable RNA species: 35S (genome-length) RNA and 21S RNA, with apparent sequence *env-c*-poly(A). Since *gag* and *pol* sequences were detected only in genome-length RNA's, it seems likely that the full-length transcripts function as messenger RNA for these two genes. The 28S and 21S RNA's could be the active messengers for the *env* and *src* genes. Analyses of sequence homologies among nucleic acids of different avian oncoviruses demonstrated substantial similarities within most of the genetic regions of these viruses. However, the common region of Rous-associated virus-O, an endogenous virus, differed significantly from that of the other viruses tested. (67 refs.)

- 77-5706 **Modification of the Lipid Composition of Normal and Rous Sarcoma Virus-infected Cells. Effects on Transformation-associated Membrane Properties.** (Eng.) Hale, A. H. (Center Cancer Biology, Massachusetts, Inst. Technology, Cambridge, MA 02139); Pessin, J. E.; Palmer, F.; Weber, M. J.; Glaser, M. *J Biol Chem* 252(17): 6190-6200; 1977.

To investigate the role of membrane lipids in transformation-associated membrane changes, the effects of lipid modification on cell surface-related properties of chicken embryo fibroblasts, either normal or infected with Rous sarcoma virus (RSV), were analyzed. Normal and infected cell growing in delipidated medium containing either polar head group analogs or specific fatty acids displayed similar lipid alteration kinetics. Lipid modification was 50% complete in 10 hr. It had little or no effect on the rate of hexose transport by normal or RSV-transformed cells, except for supplementation with ethanolamine, which caused a slight drop in transport in normal cells. Lipid modification did, however, exert several effects on cell substrate adherence, the most marked one being a decreased adherence in normal cultures without any choline analog or in those supplemented with 1-2-amino-1-butanol, ethanolamine, or N-methylethanolamine. A profound change in morphology accompanied the decreased adherence in the 1-2-amino-1-butanol-supplemented cultures. The cells became round and refractile, with numerous blebs, ruffles, and microvilli on their surface. 1-2-Amino-1-butanol supplementation changed the normal cells into partial

phenocopies of RSV-transformed cells with respect to their adhesiveness and morphology. (55 refs.)

- 77-5707 **Solubilization of Initial Attachment Site Activity for Tumor Viruses with Lithium Diiodosalicylate.** (Eng.) Moldow, C. F. (Dept. Medicine, Univ. Minnesota Medical Sch., Minneapolis, MN 55455); McGrath, M.; Peterson, C. *Proc Soc Exp Biol Med* 154(2): 201-205; 1977.

The membrane components of cultured chick embryo fibroblasts (CEF) were solubilized by suspending 5-10 mg CEF plasma membranes with 0.3 M buffered lithium 3,5-diiodosalicylate (LIS). They were then incubated with Rous sarcoma virus (RSV), with its Rous-associated virus envelope RSV(RAV-1) (5×10^5 focus forming units), for 30 min at 4 C. Discontinuous sucrose gradient centrifugation indicated that attachment was consistently reduced by the CEF LIS extract. For example, a 55% reduction in RSV(RAV-1) binding occurred after the virus was incubated with 19 μ g of CEF LIS extract. Similar results were obtained with RSV(RAV-2). Inhibition appeared to be linear to 10 μ g (neutral sugar), and then the blocking efficiency of the extract decreased. Preincubation of RSV(RAV-1) with 50 μ g LIS extract also reduced the infectivity of the virus. Glycophorin prepared by LIS extraction of human RBC ghosts did not antagonize the RSV(RAV-1) attachment as well as the CEF LIS extract; about 200 RBC were needed to produce the activity of a single CEF. Constituents of LIS extract may bind to avian tumor virus surface glycoproteins, preventing subsequent binding of the virus to its membrane site and reducing the viral transforming capacity. (12 refs.)

- 77-5708 **Differential Expression of Relevant Rous Sarcoma-associated Antigens in Cultured Cells.** (Eng.) Wainberg, M. A. (Lady Davis Inst. Medical Res., Jewish General Hosp., Montreal, Quebec); Israel, E.; Schwartz-Luft, E.; Yu, M. *Cancer Res* 37(9): 3026-3033; 1977.

The interactions of lymphocytes of chickens bearing Rous sarcoma virus (RSV)-induced tumors with normal chicken embryo fibroblast (CEF) cells, RSV-transformed CEF cells, and RS tumor cells derived from growing neoplasms, as well as with 3 M KCl extracts and supernatant fluids of each of these cell types, were examined. Cytotoxicity studies using splenic lymphocytes from tumor-bearing chickens showed that the RS tumor cells were far more susceptible to the cytotoxicity than the RSV-transformed CEF cells, which, in turn, were more susceptible than the normal CEF. In peripheral lymphocyte stimulation studies, a significant blastogenesis response was seen with 3 M KCl extracts of both RS cells and transformed CEF cells, but, for the supernatant fluids, significant reactivity was detected only when material derived

from cultures of transformed CEF cells was used. Although the results indicate a different expression of relevant detectable tumor-associated antigens in these various cell types, it could not be determined whether viral or nonviral antigens were involved. Morphological studies of these cells by scanning electron microscopy revealed that the transformed CEF and RS cells had a round shape, many surface microvilli, and extensive ruffling and blebbing of the cell membrane. Normal CEF cells were fusiform, with relatively smooth surfaces and a paucity of microvilli. There was no significant morphological distinction between the two neoplastic cell variants. (31 refs.)

77-5709 Avian Oncornavirus Reverse Transcription In Vitro: The Mechanism of Proviral DNA Synthesis (Meeting Abstract). (Eng.) Collett, M. S. (Univ. Michigan, Ann Arbor, MI 48104). *Diss Abstr Int [B]* 38(3): 1054; 1977. (no refs.)

77-5710 Expression of Viral Components in Avian Sarcoma Virus-transformed Mammalian Cells (Meeting Abstract). (Fre.) Vigier, P. (Institut du Radium, Faculte des Sciences, 91400 Orsay, France); Aupoix, M.; Chignol, M. C. *Ann Immunol (Paris)* 128C(4/5): 958; 1977. (no refs.)

77-5711 Presence of Tumor Specific Surface Antigen (TSSA) in the Culture Medium of Rat Cells Transformed by Avian Sarcoma Viruses (Meeting Abstract). (Fre.) Aupoix, M. (Unite de Virologie Fondamentale et Appliquee, INSERM U. 51, Groupe de Recherches CNRS no 33.1, place Professeur-Joseph-Renaut, 69371 Lyon Cedex 2, France); Laurent, J. C.; Greenland, T.; Krsmanovic, V. *Ann Immunol (Paris)* 128C(4/5): 937-938; 1977. (no refs.)

77-5712 Studies on the Origin and Evolution of the Transforming Gene of Avian Sarcoma Viruses (Meeting Abstract). (Eng.) Stehelin, D. (INSERM, U.102, Place de Verdun, 59045 Lille, France); Roussel, M. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 49; 1977. (no refs.)

77-5713 Susceptibility of Turkeys to Georgia Strain of Marek's Disease Virus of Chicken Origin. (Eng) Paul, P. S. (Coll. Veterinary Medicine, Univ. Minnesota, St. Paul, MN 55108); Sautter, J. H.; Pomeroy, B. S. *Am J Vet Res* 38(10): 1653-1656; 1977.

The susceptibility of turkeys to the Georgia strain (GA) of Marek's disease virus (MDV) was determined in two experiments. One-day-old chickens and turkeys were inoculated with 0.2 ml of Marek's disease (MD) infective plasma or tumor homogenate and raised in isolation for 29 wk. The MDV inocula were pathogenic for chickens and turkeys and caused high mortality (chickens, 100%; turkeys, 70%). Macroscopic lesions of MD were observed in the liver, spleen, lungs, proventriculus, and other visceral organs. Microscopically, the affected tissues were infiltrated with a pleomorphic population of neoplastic lymphocytes. Uninoculated turkeys did not show gross microscopic MD lesions. MDV was reisolated from the inoculated, but not from the uninoculated, chickens and turkeys. Antibodies to MDV were detected in the experimentally infected chickens. Uninoculated chickens and all turkeys lacked precipitating antibodies to MDV. This study suggests that turkeys are highly susceptible to experimental infection with the GA strain of MDV. (23 refs.)

77-5714 Nucleotide Sequences Derived from Pheasant DNA in the Genome of Recombinant Avian Leukosis Viruses with Subgroup F Specificity. (Eng) Keshet, E. (McArdle Lab. Cancer Res., Univ. Wisconsin-Madison, Madison, WI 53706); Temin, H. M. *J Virol* 24(2): 505-513; 1977.

Nucleic acid hybridization studies were performed to study the genome of Rous-associated virus 61 [RAV-61; a recombinant between Bryan high-titer strain of Rous sarcoma virus (RSV) and normal pheasant DNA] and another RAV with subgroup F specificity (RAV-F) obtained by passage of RSV-RAV-O in ring-necked pheasant embryo cells. Approx 20% to 25% of the genome of these viruses was acquired genetic information that was not shared by the parent virus. Furthermore, RAV-F genomes had nucleotide sequences homologous to some pheasant nucleotide sequences that were also present in the parent viruses. A complementary DNA containing only nucleotide sequences complementary to those acquired by RAV-61 through recombination was prepared. These sequences were all pheasant-derived and were not present in genomes of reticuloendotheliosis viruses, pheasant viruses, or the avian leukosis-sarcoma viruses of subgroups A, B, C, D, and E. They were, however, partially endogenous to DNA from chicken and quail in proportion to their relatedness to the pheasant. There was a great deal of homology between pheasant nucleotide sequences and related nucleotide sequences in the DNA of normal chickens. It was not possible to assign the pheasant-related sequences to any viral gene. (21 refs.)

77-5715 Endogenous RD-114 Virus Genome Expression in Malignant Tissues of Domestic Cats. (Eng) Niman, H. L. (Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA 90033); Gardner, M. B.;

Stephenson, J. R.; Roy-Burman, P. *J Virol* 23(3): 578-586; 1977.

The levels of expression of viral RNA (transcriptional level) and p30 (translational level, the major internal protein) of either endogenous C-type virus RD-114 or infectious feline leukemia virus (FeLV) in nonmalignant, lymphoma, sarcoma, and carcinoma tissues of cats were measured by molecular hybridization and competition radioimmunoassays, respectively. In contrast to normal tissues, the levels of both RNA and p30 of RD-114 virus were considerably higher in lymphoma, sarcoma, and carcinoma tissues, irrespective of the levels of FeLV expression. Thus, RD-114 RNA expression was not merely due to simple activation by FeLV. FeLV expression was generally low or undetectable except in the lymphomas, which reflected the presence of infectious FeLV. In most of the tissues tested, RNA expression of RD-114 or FeLV was usually associated with p30 detection. Results suggest that endogenous viral genes may be functionally involved in various types of neoplasia of their natural hosts. (40 refs.)

77-5716 Feline Leukemia Virus: Biochemical and Immunological Characterization of gag Gene-coded Structural Proteins. (Eng) Khan, A. S. (Viral Oncology Program, NCI, Frederick Cancer Res. Center, Frederick, MD 21701); Stephenson, J. R. *J Virol* 23(3): 599-607; 1977.

Low-mol wt, nonglycosylated structural proteins were isolated from 10 mg of feline leukemia virus (FeLV) by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and characterized immunologically by competition immunoassays. All four gag gene-coded products, a 30,000-mol wt major internal antigen (p30), a 15,000-mol wt protein (p15), a 12,000-mol wt acidic protein (p12), and a 10,000-mol wt basic protein (p10), could be quantitated by measuring their antigenic reactivity. Structural proteins of FeLV and Rauscher murine leukemia virus of corresponding mol wts possessed similar ionic properties or isoelectric point values and shared immunologically cross-reactive antigenic determinants, indicating that both may be derived from a common progenitor. In mink cells nonproductively transformed by feline sarcoma virus, p12 and p15 were expressed in the form of a common 25,000-mol wt precursor. In view of these findings, a sequence of NH₂-p15-p12-p30-p10-COOH is proposed as the internal arrangement of the FeLV gag gene. (31 refs.)

77-5717 Detection and Evaluation of Feline Oncornavirus-induced Cell Surface Antigen(s) Shed from Cells In Vitro. (Eng) Wolff, L. H. (Ohio State Univ., Dept. Veterinary Pathobiology, Columbus, OH 43210); Mathes, L. E.; Schaller, J. P.; Hoover, E. A.; Olsen, R. G. *Cancer Res* 37(11): 4134-4137; 1977.

A method for preparing soluble feline oncornavirus-induced

cell-surface antigens is described. The technique relies on the natural release of antigen(s) from FL-74 feline lymphoblastoid cells during their maintenance at 37 C in serum-deficient medium. When concentrated and clarified spent medium from 4-day cultures was tested for its antigen content by inhibition of humoral cytotoxicity, this natural production of soluble antigen was found to provide more feline oncornavirus-associated cell membrane antigen per cell than a solubilization procedure in which papain was used. The shed-antigen preparation was immunogenic in cats, eliciting humoral antibody that was reactive with the surface of FL-74 cells and feline sarcoma virus-transformed nonproducer mink cells. However, it was not reactive with feline leukemia virus in a virus neutralization assay. (38 refs.)

77-5718 Studies of Naturally Transmitted Feline Leukemia Virus Infection. (Eng) Pedersen, N. C. (Dept. Medicine, Sch. Veterinary Medicine, Univ. California, Davis, CA 95616); Theilen, G.; Keane, M. A.; Fairbanks, L.; Mason, T.; Orser, B.; Chen, C. H.; Allison, C. *Am J Vet Res* 38(10): 1523-1531; 1977.

Twenty-six 16-wk-old kittens were housed in intimate contact with asymptomatic feline leukemia virus carrier cats for 30 wk. After 30 wk of exposure, the overall infection rate was 100% and the mortality was 19%. Two cats died of bone marrow suppression, 2 of feline infectious peritonitis, and 1 of reticuloendotheliosis. Viremia developed within 3-28 wk in 22/26 cats, but the 4 remaining cats were never detectably viremic. Of these 22 cats, 6 were only transiently viremic but 16 became persistently viremic. A variable depression in the concentrations of blood platelets, WBC, and RBC occurred during the initial viremic phase. Except for several cats that died, the hematologic changes were transient. After 30 wk, all surviving cats, even those with viremia, had normal hematologic values and were clinically asymptomatic. Feline oncornavirus-associated cell membrane antigen (FOCMA) antibody appeared in the serum 2-28 wk after exposure. The titers were moderate in cats that were never viremic and high in cats that were only transiently viremic. The persistently viremic cats usually developed low or undetectable amounts of FOCMA antibody. Virus-neutralizing antibody appeared at about the same time as FOCMA antibody, and the amounts of neutralizing antibody paralleled the FOCMA antibody values. (27 refs.)

77-5719 Detection of Bovine Leukemia Virus Infection by Early Polykaryocytosis Inhibition: Results of a Seroepidemiologic Survey (Meeting Abstract). (Fre.) Mamoun, R. (Unite de Recherches de Radiobiologie Experimentale et de Cancerologie, INSERM U 117, 33076 Bordeaux Cedex, France); Guillemain, B.; Levy, D.; Astier, T.; Parodi, A. L. *Ann Immunol (Paris)* 128C(4/5): 957; 1977. (no refs.)

- 77-5720 **Morphogenesis of Bovine Leukemia Virus.** (Eng.) Calafat, J. (Dept. Electron Microscopy, Netherlands Cancer Inst., Sarphatistraat 108, Amsterdam, Netherlands); Ressang, A. A. *Virology* 80(1): 42-53; 1977.

Electron microscopy was used to study the morphogenesis of bovine leukemia virus (BLV) in short-term cultures (STC) of WBC from cows with persistent lymphocytosis and in three BLV-producing cell lines (from cows and sheep) growing as monolayers (MC). The morphology of BLV in the STC and MO was identical, indicating that it is independent of the host cell. The yield of virus particles was higher in STC, as clusters of numerous particles were found outside the WBC, but in the MC only small groups were present. Budding particles were scarce in both STC and MC. They consisted of a single shell (40-80 Å) underneath the cell surface or vacuole membrane. This shell increased in size, and attached to the concave surface. Two ensuing pathways of development are proposed: (1) condensation of the granules into a nucleoid, followed by budding from the membrane as a mature virion, or (2) budding from the membrane to give rise to a free immature particle. However, because of the low numbers of budding particles on the membrane, condensation of electron-dense material within the cytoplasm resembling virus particles in the first stage of budding, and immature and mature particles lying free in the cytoplasm, an alternative pathway is proposed. By this pathway, immature and mature particles are formed within the cytoplasm without budding. Immunoferritin studies of BLV-producing cells have shown that both bovine and goat anti-BLV sera contain antibodies against BLV. However, the cell surface was only rarely labeled and then in small areas, indicating that few viral structural polypeptides are present on the cell surface. Comparison studies showed that the morphogenesis of BLV is different from that of B- and C-type viruses and other particles such as Mason-Pfizer monkey virus and guinea pig leukemia virus. (25 refs.)

- 77-5721 **Bovine Leukemia Virus Specific Antibodies among French Cattle. II. Radioimmunoassay with the Major Structural Protein (BLV p24).** (Eng.) Levy, D. (Laboratoire d'Immunologie et de Virologie des Tumeurs, INSERM U 152, Hôpital Cochin, 27, rue du Faubourg Saint-Jacques, 75674 Paris Cedex 14, France); Deshayes, L.; Parodi, A. L.; Levy, J. P.; Stephenson, J. R.; Devare, S. G.; Gilden, R. V. *Int J Cancer* 20(4): 543-550; 1977.

A radioimmunoassay (RIA) for the major internal protein of bovine leukemia virus (BLV p24) was established using natural anti-BLV p24 antibodies and purified ¹²⁵I-labeled BLV p24. The final precipitation of the immune complexes was realized by a preparation of inactivated *Staphylococcus aureus* Cowan I. Sera from 363 cows belonging to (1) leukemic herds, (2) nonleukemic but BLV-exposed herds, and (3) apparently unexposed herds were studied comparatively by BLV p24 RIA, complement fixation, and immunodiffusion.

The BLV p24 RIA appeared much more sensitive than the two other methods in detecting positive sera. With this method, 100% of the leukemic animals, excluding those with juvenile lymphosarcoma, presented very high antibody titers ($\geq 10,000$). Practically all cows with persistent lymphocytosis were also positive with slightly lower levels of antibodies, confirming the relationship between BLV infection and persistent lymphocytosis. Moreover, about two-thirds of the hematologically suspect animals and one-third of the normal animals from BLV-exposed herds were positive, whereas 100% of the sera from unexposed cows remained negative for anti-BLV p24 antibodies. (25 refs.)

- 77-5722 **Fetal Infection with Bovine Leukemia Virus in Sheep.** (Eng.) Onuma, M. (Faculty Veterinary Medicine, Hokkaido Univ., Sapporo, Japan); Baumgartner, L. E.; Olson, C.; Pearson, L. D. *Cancer Res* 37(11): 4075-4081; 1977.

Sheep fetuses were thymectomized, and their tails were removed at 58-65 days of gestation for tissue culture. Bovine leukemia virus (BLV) antigens were detected in serial culture of tissues from fetuses whose dams and sires were BLV-positive. However, no BLV antigens were detected in serial cultures of tissues from fetuses whose dams were negative but whose sires were positive. Precolostral sera from 3/16 neonatal lambs, whose sires and dams were both BLV-positive, were BLV-antibody-positive. Thus, BLV may be transmitted vertically from a positive dam to her lamb via the placenta and/or germinal cells, but not from sire to lamb. (36 refs.)

- 77-5723 **Oncogenic and Nononcogenic Bovine Adenoviruses and Guanine-Cytosine Content of Their DNA.** (Eng.) Panigrahy, B. (Dept. Veterinary Microbiology, Coll. Veterinary Medicine, Texas A&M Univ., College Station, TX 77843); McCormick, K. J.; Trentin, J. J. *Am J Vet Res* 38(8): 1151-1152; 1977.

Bovine adenoviruses types 1 (BAV-1), 2 (BAV-2), and 3 (BAV-3) were purified and tested for oncogenicity in newborn Syrian hamsters (LSH/Lak). The hamsters were inoculated sc with 0.1 ml of one of the virus preparations. BAV-3 was highly oncogenic (21/21 animals developed tumors with a mean latent period of 38 days), but BAV-1 and BAV-2 were nononcogenic (0/37 and 0/42 animals, respectively, had developed tumors within the 18-mo observation period). The tumors were undifferentiated sarcomas. The DNA of BAV-3 had a guanine + cytosine (G+C) content of 48%, whereas the nononcogenic BAV-1 and BAV-2 had a G+C content of 61% to 62%. Thus, the G+C content of these three BAV's, like the human adenoviruses, are inversely correlated with their oncogenicity. (20 refs.)

- 77-5724 **Virus-induced Specific Cell Surface Antigen(s) on Mouse Adenovirus-infected Cells.** (Eng) Inada, T. (Dept. Serology and Immunology, Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan); Uetake, H. *Infect Immun* 18(1): 41-45; 1977.

A virus-specific cell-surface antigen(s) was detected on murine adenovirus-infected C3H mouse embryo cells. It also was demonstrated in infected HeLa cells. It became detectable on the cell surface about 6 hr postinfection and was present in 90% of infected cells at 24-36 hr postinfection. In contrast, intracellular capsid antigens became detectable at 24 hr postinfection. Since the surface antigen was also detected on virus-infected cells treated with 5'-fluoro-deoxyuridine to block viral DNA synthesis, it was synthesized early in infection and may not be a virus structural component. The relationship between this serologically detectable cell surface antigen(s) and the cell-mediated immune response to virus infections is discussed. (16 refs.)

- 77-5725 **RNA Tumour Virus Phosphoproteins: Evidence for Virus Specificity of Phosphorylation.** (Eng) Hayman, E. G. (Dept. Pathology, University of Southern California Sch. Medicine, Los Angeles, CA 90033); Pal, B. K.; Roy-Burman, P. *J Gen Virol* 36(3): 459-469; 1977.

The purified 12,000-dalton (p12) phosphoprotein of Rauscher (R) and wild mouse (WM) strains of murine leukemia virus (MuLV) was analyzed for the distribution patterns of its variously charged molecular species by urea-polyacrylamide gradient gel electrophoresis. The distribution patterns of the p12 of two different field isolates of WM viruses, 292 and 1504, and the mouse-tropic and amphotropic clonal subpopulations of the 1504 isolate were similar; they differed from that of the p12 of MuLV-R. A unique characteristic of the p12 of the WM was the presence of two major apparently nonphosphorylated species. Similar studies on the p12 of the same virus (MuLV-R or WM viruses) grown in different host cells showed that the phosphorylated and nonphosphorylated species are virus-specific and independent of the cell lines of propagation. These analyses and their comparison with urea-gel patterns of the phosphoproteins of other mammalian C type viruses indicated that the number and relative proportion of the phosphorylated and nonphosphorylated species are predetermined for a virus. Therefore, the virus must have the genetic information for the phosphoprotein, as well as other necessary genetic information that functions in regulating the specific proportions of these multiple species. The possible biological significance of the variously charged molecular species in the phosphoprotein of RNA tumour viruses is discussed. (19 refs.)

- 77-5726 **Synthesis and Cleavage of Rauscher Leukemia Virus Precursor Proteins in Synchronized Cells.**

(Eng) Naso, R. B. (Biology Dept., Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Brown, R. L. *Virology* 82(1): 247-251; 1977.

The cell cycle-dependent variations in the synthesis and cleavage of Rauscher murine leukemia virus (R-MLV) precursor proteins are described, and a comparison is made with total protein synthesis. There were three waves of viral precursor protein synthesis corresponding to G₁, middle S, and late S-G₂. The latter two waves of synthesis lagged approx 1 hr behind the two waves of DNA synthesis. The last wave occurred approx 1-2 hr before mitosis. During these times, synthesis of viral-specific proteins amounted to 4.5%-5.5% of the total cell protein synthesis; it dropped to <2% at other times in the cell cycle. The mid-S and late S-G₂ waves apparently were dependent upon the presence of newly synthesized viral RNA. High-resolution gel electrophoresis of immunoprecipitates from pulse-labeled and pulsed, chase-incubated cells identified the viral-specific proteins made in each wave as those precursors and viral cleavage products characteristic of nonsynchronized cells infected with R-MLV. (21 refs.)

- 77-5727 **Induction of Transmissible Leukemialike Syndromes in Mice by Injection of Antigens and Immunostimulants.** (Rus.) Denner, I. (Lab. Immunochimistry and Tumor Diagnostics, N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR). *Biull Eksp Biol Med* 84(9): 344-346; 1977.

Adult male BALB/c mice were injected with either a mixture of a virus-free plasma fraction (supernatant) or of viruslike particle-containing sediment from mice with Rauscher leukemia plus bovine γ -globulins in Freund's complete adjuvant or dextran sulfate. Most animals developed marked splenomegaly after the fifth injection. The spleen showed highly pronounced myeloid metaplasia and increased numbers of megakaryocytes and erythroblasts. The percentage of peroxidase-positive cells was 20%-50% vs a control value of 11%-12%. The leukemialike syndrome could be transmitted to adult mice by inoculating them with spleen cells or plasma from mice with the syndrome. Increased numbers of peroxidase-positive and sudanophilic cells, foci of erythropoiesis, and large numbers of megakaryocytes and activated follicles were seen. Perivascular reactive infiltrates consisting of myeloid, lymphoid, and histiocytic cells and circulatory disorders were found in the liver and other organs. Anemia and leukopenia were found 14 days after injection. Slight leukocytosis remained after normalization of the other parameters during the sixth week. The animals usually died within 3 mo with splenomegaly. Some animals died after 4 mo with leukocytosis (6,000/mm³, mainly myeloid cells and blasts); and leukemic infiltrates consisting of myeloid cells were found in all organs. The supernatant of the plasma was ineffective, which indicates the corpuscular nature of the inducing agent. The plasma sediment from the mice with leukemialike syndrome

77-5727-77-5734

contained viruslike particles with a diameter of 30-50 nanometers. C-type RNA viruses but no viruslike particles were found in the spleen cells. (11 refs.)

77-5728 Formation of Translational Precursor Polypeptides to p30 During Replication of the Rauscher Murine Leukemia Virus in JLS-V10 Cells (Meeting Abstract). (Eng.) Robinson, O. R. (Univ. Massachusetts, Amherst, MA 01002). *Diss Abstr Int [B]* 38(4): 1573-1574; 1977. (no refs.)

77-5729 Cellular and Serum Involvement in Protection Against Friend Leukemia Virus. (Eng) Schuller, G. B. (Dept. Surgery, Medical Coll. Virginia, Virginia Commonwealth Univ., Richmond, VA 23298); Morahan, P. S. *Cancer Res* 37(11): 4064-4069; 1977.

Treatment of BALB/c mice with the immunomodulator pyran copolymer (25 mg/kg ip, for 5 days) inhibited leukemogenesis produced by the Friend leukemia virus (FLV) complex, as evidenced by inhibition of the spleen focus-forming virus (SFFV) and lymphatic leukemia virus (LLV), as well as by a significant decrease in splenomegaly. The protective effect of pyran appeared to be mediated by macrophages. Protection was conferred on normal recipient mice when peritoneal exudate cells from pyran-treated mice were transferred to recipient mice infected 24 hr later with FLV. Animals receiving pyran-activated peritoneal cells had a significant reduction of splenomegaly and of SFFV and LLV titers compared with control animals. In contrast, when glycogen-elicited peritoneal exudate cells were transferred, the mice were not protected. Pyran-activated peritoneal cells, but not normal peritoneal cells, also inhibited FLV growth in vitro. Serum from pyran-treated, but not glycogen-treated, mice also transferred resistance to FLV-infected mice. (35 refs.)

77-5730 Biochemical and Immunological Characterization of Two Distinct Variants of Histone H2A in Friend Leukemia. (Eng) Blankstein, L. A. (Dept. Medicine, Tufts Univ. Sch. Medicine, Boston, MA 02111); Stollar, B. D.; Franklin, S. G.; Zweidler, A.; Levy, S. B. *Biochemistry* 16(21): 4557-4562; 1977.

Changes in the relative amount of two histone H2A subfractions were observed in cells at different proliferative stages of Friend leukemia. Biochemical analyses of the purified H2A subfractions showed that they differed in primary structure and were not the result of postsynthetic modifications of the same parent protein. Antibodies against the purified H2A2 subfraction crossreacted with H2A1 and H2A2 but showed high specificity for the immunizing subfraction at

higher sera dilutions. H2A2 contained a methionine that appeared to be responsible for the antigenic differences between H2A2 and H2A1. The change in the relative amounts of two nonallelic variants of a histone coincident with changes in the physiologic states of the cell may indicate a correlation between genome structure and function. (34 refs.)

77-5731 Spontaneous Regression of Friend Virus-induced Erythroleukemia. II. Regression of Friend Murine Leukemia Virus-induced Lymphocytic Leukemia. (Eng) Dietz, M. (Dept. Biology, Michigan Cancer Foundation, Detroit, MI 48201); Longley, C.; Fouchey, S. P.; Hall, L.; Rich, M. A.; Furmanski, P. *J Natl Cancer Inst* 59(3): 957-961; 1977.

The spontaneous regression of Friend murine leukemia virus (MuLV)-induced lymphocytic leukemia was studied. Regression occurred in 16/47 leukemic Swiss/ICR, 2/10 NIH/Swiss, 2/5 N/PLCR, 3/9 SIM, and 9/9 BALB/c mice infected with helper MuLV derived from regressing Friend virus complexes (RFV). Lymphoid organs returned to near normal wts and histology, the animals recovered from anemia, and a 10- to 1,000-fold decrease in virus titer was seen. The sera of mice in which leukemia regressed contained potent virus-neutralizing activity associated mainly with immunoglobulins. These findings support the view that the regressing phenotype of RFV is due to its helper MuLV component. (29 refs.)

77-5732 Effect of Friend Complex Viruses on the Development of Cells Forming Natural Antibodies In Vitro (Meeting Abstract). (Ita.) Bendinelli, M. (Istituto di Microbiologia, Universita de Pisa, Pisa, Italy); Toniolo, A. *Ann Sclavo* 18(6): 876-877; 1976. (4 refs.)

77-5733 C-type RNA Tumour Viruses: Isolation and Characterization of a Complete DNA Copy of the Erythroid-specific Friend Virus Genome (Meeting Abstract). (Eng.) Pragnell, I. B. (Beatson Inst. for Cancer Res., Wolfson Lab. for Molecular Biology, Glasgow, Scotland); Ostertag, W.; Paul, J. *Br J Cancer* 36(3): 410; 1977. (3 refs.)

77-5734 The Expression of Viral and Globin Genes During Differentiation of the Friend Cell. (Eng.) Pragnell, I. B. (Beatson Inst. for Cancer Res., Wolfson Lab. Molecular Pathology, Gartcube Estate, Bearsden, Glasgow, G61 1BD, Scotland); Ostertag, W.; Paul, J. *Exp Cell Res* 108(2): 269-278; 1977.

The expression of viral and globin genes was investigated using the erythroleukemic F4 cell line, its subclone F4-6, the bromodeoxyuridine resistant TK- subclone B8 and its subclone B8/3. A five-fold increase in globin messenger (m)RNA synthesis was observed 2 days after induction of Hb synthesis by dimethylsulfoxide (DMSO) in F4-6 virus positive cells. This progressed to a 100-fold increase by day 4. The amount detected in the cytoplasm was identical with that found in polysomal RNA. An increase in viral RNA preceded the max increase in globin RNA; these findings suggest a high basal level of virus specific RNA in these cells. In clone B8/3, titration of cytoplasmic RNA with complementary viral DNA showed no major changes in virus specific RNA either in the polysomes, where it was present in large amounts, or in the cytoplasm. The entire increase in globin mRNA accumulation was noted within only 2 days in these cells; furthermore, there was a higher basal level of this mRNA in B8/3 compared with values for other cell lines. There was a good correlation between the timing of max virus release and the max viral RNA accumulation in the cytoplasm and polysomes. Clone B8/3 did not release significant amounts of spleen focus forming virus following DMSO induction of differentiation, and electron microscopy did not reveal any C type viruses. (42 refs.)

77-5735 Analysis of MuLV Populations Involved in Radiation Induced Leukemia in C57BL Mice (Meeting Abstract). (Eng) Astier, T. (INSERM, U 117, 33076 Bordeaux, France); Guillemain, B.; Janowski, M.; Mamoun, R.; Duplan, J. F. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977.* International Agency for Research on Cancer. (Lyon France): p. 59; 1977. (no refs.)

77-5736 Genetic Control of Radiation Leukemia Virus-induced Tumorigenesis. I. Role of the Major Murine Histocompatibility Complex, H-2. (Eng) Meruelo, D. (Div. Immunology, Dept. Medicine, Stanford Univ. Sch. Medicine, Stanford, CA 94305); Lieberman, M.; Ginzton, N.; Deak, B.; McDevitt, H. O. *J Exp Med* 146(4): 1079-1087; 1977.

C57BL/10-derived H-2 congenic and recombinant strains of mice were examined for their susceptibility to leukemia induced by intrathymic inoculation of radiation leukemia virus (RadLV, 0.05 ml/lobe). Resistance to RadLV-induced leukemogenesis was associated with the H-2D region of the H-2 complex or with closely linked loci. The H-2Dd allele conferred resistance to the disease, but the H-2Dq and H-2Ds alleles were associated with susceptibility. The possibility that the H-2-linked resistance is due to mechanisms other than Ir genes is discussed. (28 refs.)

77-5737 Genetic Control of Radiation Leukemia Virus-induced Tumorigenesis. II. Influence of Srv-1, a Locus Not Linked to H-2. (Eng) Meruelo, D. (Div. Immunology, Dept. Medicine, Stanford Univ. Sch. Medicine, Stanford, CA 94305); Lieberman, M.; Deak, B.; McDevitt, H. O. *J Exp Med* 146(4): 1088-1095; 1977.

Although they carry the H-2Dd allele, which is associated with resistance to the disease, B10.AQR mice are highly susceptible to radiation leukemia virus (RadLV)-induced leukemogenesis. F₂ segregation analysis and studies with B10.AQR(n8) mice indicated that a single locus, designated Srv-1, confers dominant susceptibility to RadLV. The locus is not linked to H-2, and it appears to be distinct from Fv-1 and Fv-2. Preliminary data suggest that Srv-1 affects virus proliferation. (19 refs.)

77-5738 Expression of a Gross Virus Associated Cell Surface Antigen by Radiation Leukaemia Virus (RadLV/Rs) Infected Cells (Meeting Abstract). (Eng) Gerlier, D. (Centre Leon Berard, 69273 Lyon Cedex 2, France); Guillemain, B.; Dore, J. F.; Duplan, J. F. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977.* International Agency for Research on Cancer. (Lyon, France): p. 59; 1977. (no refs.)

77-5739 Presence of Complement-fixing Antibodies Against Antigens of Gross Virus-induced Rat Lymphoma and Normal Rat Thymus in Sera of Patients with Some Forms of Malignancies. (Eng) Simkovic, D. (Cancer Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia); Chorvath, B.; Hlubinova, K.; Valentova, N.; Stevonkova, J.; Babusikova, O.; Simkovicova, M. *Neoplasma* 24(4): 357-363; 1977.

The presence of antibodies against soluble antigens of Gross murine leukemia virus-induced rat lymphoma W/Fu(C58NT)D and normal rat thymus antigens was examined in the sera of 180 healthy subjects, 100 healthy pregnant women, 64 patients with acute myelosis, lymphadenosis, and acute undifferentiated leukemia, 15 patients with chronic myelosis and lymphadenosis, and 60 patients with Hodgkin's disease. The following were positive for C58 antigen: 17/180 healthy subjects, 22/100 pregnant women, 33/64 patients with myelosis, lymphadenosis, and acute undifferentiated leukemia, 0/15 of the chronic leukemia group, and 15/60 Hodgkin's disease patients. Eleven sera with positive reactions against C58 were tested for reaction with rat thymus antigens. The 3 control group, 4 Hodgkin's disease and 3 acute leukosis samples all gave the same results as those obtained with C58, suggesting a similarity in antigenic determinants. Sera from eight patients positive for C58 were tested before and after absorption with pooled normal human lymphocytes; the antibodies in the sera were not absorbed by this

treatment. The significance of these findings is discussed. (18 refs.)

77-5740 Bone Marrow Colony-forming Cells in Mice with Virus-induced Lymphoid Leukemia: Relation to Serum Colony-stimulating Activity and Blood Granulocytes. (Eng) Foster, R. S. (Univ. Vermont Coll. Medicine, Dept. Surgery, Given Building, Burlington, VT 05401). *J Natl Cancer Inst* 58(5): 1503-1505; 1977.

The relationships between serum colony-stimulating activity (CSA) elevation, bone marrow in vitro colony-forming cells (CFC), and peripheral blood granulocytes in Swiss mice with advanced lymphoid leukemia induced by a virus were studied. Mice with advanced lymphoid leukemia had elevated peripheral blood granulocytes and elevated serum CSA, which promotes the in vitro growth of granulocyte and/or macrophage colonies. The number of bone marrow precursor cells of the in vitro granulocyte and/or macrophage colonies varied from normal to 10% of normal. There was no correlation between the percentage of leukemia cells in the bone marrow and serum CSA nor between the degree of elevation of CSA and the elevation of blood granulocytes in individual mice. The elevation of CSA correlated best with a combination of increased blood granulocytes and a deficiency of bone marrow precursor cells, suggesting that CSA is a leukopoietin that increases the efficiency and production of granulocytes. (14 refs.)

77-5741 Interactions of Murine Leukemia Virus Core Components: Characterization of Reverse Transcriptase Packaged in the Absence of 70S Genomic RNA. (Eng) Gerwin, B. I. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD 20014); Levin, J. G. *J Virol* 24(2): 478-488; 1977.

The role of genomic RNA in the capsule formation of functional reverse transcriptase was studied by comparing the properties of the reverse transcriptase enzymes in normal and actinomycin D-treated AKR-L1 virions from SC-1 cells. Chromatographic analyses, template/primer preferences, and velocity sedimentation in glycerol indicated that the physicochemical properties of the two molecules were identical. The two enzymes also had equal sensitivity to inactivation by antibodies directed against Rauscher murine leukemia virus DNA polymerase and similar thermal decay rates, despite the lack of 70S genomic RNA in the actinomycin D-treated virions. These results confirm previous findings that all normal virion proteins are present in particles from actinomycin D-treated cells. It is suggested that reverse transcriptase is not associated with genomic RNA within the virion core. (31 refs.)

77-5742 Electron Microscopic Characterization of the Defectiveness of a Temperature-sensitive Mu-

tant of Moloney Murine Leukemia Virus Restricted in Assembly. (Eng) Yuen, P. H. (Dept. Microbiology, Univ. Illinois, Urbana, IL 61801); Wong, P. K. *J Virol* 24(1): 222-230; 1977.

The effect of temperature shiftdown on the assembly of ts3 virions [temperature-sensitive mutants of Moloney murine leukemia virus (Mo-MuLV)] was observed using virions cultured in TB cells and scanning (SEM) and transmission electron microscopy (TEM). SEM revealed that there were more virions on the cell surface of mutant cells grown at 39 C (nonpermissive temperature) than on those grown at 34 C (permissive temperature) or on wild-type MuLV-infected cells grown at 39 C. More than 90% of these particles disappeared from the cell surface within 1 hr after temperature shiftdown. Furthermore, there were more normal single particles than aggregates (virions with 2 or more pieces of genomic RNA) in the ts3-infected cells grown at 39 C and there were more aggregates in these cells than in mutants grown at 34 C or in wild-type MuLV-infected cells grown at 39 C. The high proportion of aggregates in the 39 C ts3 cells could be due to a higher density of budding virions at the cell surface. TEM studies indicated that although both normal particles and aggregates in different stages of assembly were present in the mutant cells at 39 C, < 20% were completely assembled. This suggests that virion production is initiated, but probably restricted. Virion assembly, with both normal particles and aggregates dissociating from the cell surface, occurred rapidly upon temperature shiftdown. It is suggested that an altered glycoprotein restricts virion assembly. (12 refs.)

77-5743 Isolation and Preliminary Characterization of Temperature-sensitive Mutants of the Murine Sarcoma Leukemia Virus Complex. (Eng) Yuasa, Y. (Dept. Tumor Virus Res., Inst. Medical Science, Univ. Tokyo, Post Office Takanawa, Tokyo 108, Japan); Shimojo, H. *J Gen Virol* 36(2): 257-266; 1977.

Five temperature-sensitive (ts) mutants of the Moloney murine sarcoma-leukemia virus complex (MSV-MuLV), as determined by the production of ts phenotypes in YH7 mouse cells, were isolated after exposure of wild-type MSV-MuLV to UV radiation (8,000 ergs/mm²) or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG, 2 mg/ml for 20 min at 36 C). Two mutants lacked heat-labile virion proteins and were temperature-independent in the postpenetration helper functions necessary for the fixation of sarcoma virus transformation in normal rat kidney cells. The remaining three ts mutants were temperature-independent both in maintaining the transformed state and in initiating colony formation in suspension. (22 refs.)

77-5744 Effect of Helper Virus on the Number of Murine Sarcoma Virus DNA Copies in Infected

Mammalian Cells. (Eng) Frankel, A. E. (Lab. Viral Carcinogenesis, NCI, Bethesda, MD 20014); Gilbert, J. H.; Fischinger, P. J. *J Virol* 23(3): 492-502; 1977.

Mouse, cat, dog, and human cell lines were transformed by Moloney murine sarcoma virus (M-MSV), and the viral DNA copies in total cellular DNA were quantitated. Sarcoma-positive, leukemia-negative (S+L-) M-MSV-transformed cells were compared with M-MSV-transformed cells infected with a replicating leukemia virus. Unfractionated M-MSV complementary (cDNA) MSV-specific cDNA, and MSV-murine leukemia virus (MuLV) cDNA were hybridized to the total cellular DNA of each species. DNA's of mouse, cat, dog, and human S+L- cells contained from < one to a few proviral M-MSV DNA copies per haploid genome. In contrast, helper virus-coinfected, M-MSV-producing cells of each species showed a 3- to 10-fold increase in M-MSV proviral DNA over that in corresponding S+L-cells. MSV-specific and MSV-MuLV common nucleotide sequences were each increased to a similar degree. A corresponding examination of cellular DNA of leukemia virus-infected normal or S+L- mammalian cells was performed to establish the resulting number of leukemia proviral DNA copies. The infection of normal or S+L- mammalian cells with leukemia helper viruses lacking nucleotide sequences closely related to those of the host cell resulted in the appearance of one to three corresponding leukemia proviral DNA copies. (41 refs.)

77-5745 **M-MSV Tumor Progression Due to Lack of Cell-Mediated Immune Response to In Vivo Newly Formed Pseudotype (Meeting Abstract).** (Eng) Chieco-Bianchi, L. (Lab. Experimental Oncology, Univ. Padova, Padua, Italy); Collavo, D.; Biasi, G.; Colombatti, A. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 53; 1977. (no refs.)

77-5746 **Prostaglandin and Cyclic Nucleotides in Moloney Sarcoma Virus Induced Tumors (Meeting Abstract).** (Eng.) Humes, J. L. (Rutgers Univ., State Univ. New Jersey, Newark, NJ). *Diss Abstr Int [B]* 38(3): 1131; 1977. (no refs.)

77-5747 **Specific Changes in the Collagen Phenotype of BALB 3T3 Cells as a Result of Transformation by Sarcoma Viruses or a Chemical Carcinogen.** (Eng.) Hata, R. (Lab. Biochemistry, NCI, Bethesda, MD 20014) Peterkofsky, B. *Proc Natl Acad Sci USA* 74(7): 2933-2937; 1977.

The types and amount of collagen (Co) synthesized by the parent BALB 3T3 A-31 lines and by transformants produced by Kirsten (Ki) or Moloney (Mo) sarcoma (RNA) and simian virus 40 (SV40) (DNA) viruses as well as by a chemical carcinogen, 4-nitroquinoline-1-oxide (NQO), were determined. ¹⁴C-proline-labeled procollagen, accumulated during a 3-hr incubation of normal and transformed cell cultures, was treated with pepsin, and the resulting Co components were analyzed by carboxymethylcellulose chromatography and sodium dodecyl sulfate/polyacrylamide gel electrophoresis in the presence or absence of reducing agent. Co in the medium of three subclones of BALB 3T3 A-31 that exhibited contact inhibition of growth at confluence and in the medium of one that did not consisted of a 3:1 ratio α_1 and α_2 subunits. This suggests that 3T3 cells synthesize Type I Co and another type designated X, composed of α_1 chains, which may or may not be identical to $\alpha_1(I)$. Culture medium from 3T3 transformed by the sarcoma viruses contained Type I and Type Y Co. The latter appeared to be similar to Type II Co, since it contained intrahelical disulfide bonds. Analysis of intracellular Co also demonstrated the presence of Type II in Ki-3T3 and its absence from 3T3 cells. Co components from the medium of an SV40 transformant were identical to those of the contact-inhibited clones, but the Co from an NQO-induced transformant was composed mainly of two components differing from $\alpha_1(I)$, α_2 , or $\alpha_1(III)$. These results suggest that the Co accumulated in transformed cell cultures may be specifically related to the transforming agent. (29 refs.)

77-5748 **The Correlation of Intracellular Cyclic AMP Content, Cell Growth, Plasma Membrane Microvilli and Exposed Surface Proteins Before and after Transformation of Normal Rat Kidney Cells (Meeting Abstract).** (Eng.) Carley, W. W. (Vanderbilt Univ., Nashville, TN 37203). *Diss Abstr Int [B]* 38(3): 1053; 1977. (no refs.)

77-5749 **Transformation of Rat Liver Epithelial Cells by Kirsten Murine Sarcoma Virus.** (Eng) Rhim, J. S. (Dept. Cancer Res., Microbiological Associates, 5221 River Road, Bethesda, MD 20016); Kim, C. M.; Okigaki, T.; Huebner, R. J. *J Natl Cancer Inst* 59(5): 1509-1516; 1977.

Kirsten murine sarcoma virus transformation of the W rat liver epithelial cell lines RL-33 and RL-34 was investigated. By day 4 or 5 after virus infection, focal piles of epithelial cells that formed small projections and released round cells from the foci were noted. These cells grew as chains or islets; an accumulation of ridges was often seen in the infected cells. At confluence, transformed cells grew in suspension above the cells attached to the bottom of the flask. The virus titration pattern was one-hit. Three types of transformed cells could be isolated with respect to virus release and antigen

expression: virus producer, nonproducer, and sarcoma-positive, leukemia-negative cells. Most of the lines were producers. Characteristics of the three types of clones are presented. Transformed cells transplanted sc into newborn W or F344 rats were tumorigenic, but untransformed cells were not. Histologically, the tumors were fibrosarcomas or poorly differentiated sarcomas. The tumors grew progressively and were transplantable. Treatment of normal rat epithelial cells with 50 μ g 5-iodo-2'-deoxyuridine resulted in the induction of RNA-dependent DNA polymerase and C-type virus particles. All attempts to grow these virus particles in mammalian cells failed. (32 refs.)

77-5750 Exclusive Involvement of H-2Db or H-Kd Product in the Interaction Between T-Killer Lymphocytes and Syngeneic H-2b or H-2d Viral Lymphomas. (Eng) Gomard, E. (Laboratoire Immunologie et Virologie des Tumeurs, Institut National de la Sante et de la Recherche Medicale, U 152 Hopital Cochin, 75014 Paris, France); Duprez, V.; Reme, T.; Colombani, M. J.; Levy, J. P. *J Exp Med* 146(4): 909-922; 1977.

Cytolysis of murine viral lymphoma cells by antimurine sarcoma virus (MSV) syngeneic T-killer lymphocytes was previously shown to be restricted by some products of the H-2 complex. The respective role of the products of different regions of the H-2 complex were studied with six H-2b and three H-2d lymphomas induced by five different C-type viruses. They were tested by the ^{51}Cr -release test against anti-MSV T-killer cells from different inbred strains of mice, including several H-2 recombinants. Tumors of the H-2b haplotype were lysed only when effectors and target cells possessed the Db region. In contrast, an identity limited to the K end of the H-2 complex was necessary and sufficient in the H-2d haplotype. An in vitro restimulation of the spleen cells with concanavalin A strongly increased the activity of in vivo-primed T lymphocytes, but it did not provide any response for in vivo-primed but nonresponder cells. Preincubation of the tumor cells with anti-H-2 sera abolished the lysis by syngeneic anti-MSV effector lymphocytes. The same results were obtained by preincubating the H-2b targets with anti-H-2Db, or the H-2d target with anti-H-2Kd. Preincubation with anti-H-2H-2Kb or anti-H-2Dd was ineffective. These results show that the T-killer/target cell interaction in the MSV system involved some products of the H-2 complex that might be different with the various H-2 haplotypes and that could vary according to the antigenic specificity. A specific association of a viral product with a normal cellular structure, directed by the H-2 region during viral budding, could explain these results. (32 refs.)

77-5751 Characterization of Gazdar Murine Sarcoma Virus by Nucleic Acid Hybridization and Analysis of Viral Expression in Cells. (Eng) Pang, R. H. (Lab.

Viral Carcinogenesis, NCI, Bethesda, MD 20014); Phillips, L. A.; Haapala, D. K. *J Virol* 24(2): 551-556; 1977.

The nucleotide sequences of Gazdar murine sarcoma virus (Gz-MSV) were compared with those of Moloney murine sarcoma virus (M-MSV) by nucleic acid hybridization experiments and analysis of viral expression in infected cells. Gz-MSV had an 86.7% homology with M-MSV. Reverse complementation studies revealed that all the M-MSV genome was present in Gz-MSV. Furthermore, MSV-specific sequences of both Gz-MSV and M-MSV shared some homology with hamster leukemia virus: the hamster virus had a 79.5% homology with Gz-MSV. Gz-MSV did not recombine with rat endogenous viral sequences in spite of its propagation in rat cells. Both rat and hamster cells infected with Gz-MSV expressed two viral proteins of 68,000 and 70,000 daltons that were immunoprecipitated by anti-p60 serum prepared from MSV(FeLV) virus. It is possible that Gz-MSV is a variant of M-MSV. (16 refs.)

77-5752 Mammary Tumors and Mammary Tumor Virus Expression in Hybrid Mice of Strains C57BL and GR. (Eng) Heston, W. E. (Lab. Biology, NCI, NIH, Bethesda, MD 20014); Parks, W. P. *J Exp Med* 146(5): 1206-1220; 1977.

Mammary tumorigenesis in genetic crosses between highly susceptible GR mice and resistant C57BL mice was highly correlated with murine mammary tumor virus expression in milk. Although the F₁ and first backcross females had a mammary tumor incidence that was consistent with a single dominant gene segregation, tumor incidence in the critical second backcross segregants disproved this hypothesis. Regardless of the first backcross parent, frequency of virus expression was approx 50% and tumor incidence was approx 15% in the second backcross populations. Genetic factors were clearly involved in the regulation of virus expression, which in turn correlated with tumor incidence and tumor latency. These complex phenotypes are best explained as threshold or quasicontinuous characteristics. As predicted from this model, the age-specific incidence of mammary tumors showed a broad peak at 14-19 mo of age, with no evidence of an early or late phase. The hematopoietic tumors that developed in the hybrids showed no correlation with virus expression or mammary tumorigenesis. (41 refs.)

77-5753 Virus-Estrogen Interactions in Mammary Tumorigenesis of C3H Mice Fed DES or Estradiol (Meeting Abstract). (Eng.) Berky, J. J. (Microbiology Res. Program, Natl. Center for Toxicological Res., Jefferson, AR). *J Toxicol Environ Health* 3(1/2): 343; 1977. (no refs.)

77-5754 Regulation of Mammary Tumor Virus Production by Prolactin in BALB/cfC3H Mouse Nor-

mal Mammary Epithelial Cells In Vitro. (Eng) Yang, J. (Cancer Res. Lab., Univ. California, Berkeley, CA 94720); Enami, J.; Nandi, S. *Cancer Res* 37(10): 3644-3647; 1977.

The hormonal regulation of murine mammary tumor virus (MTV) production was analyzed in normal mammary epithelial cells from chronically infected BALB/cfC3H mice. Cells grown on floating collagen gels consistently responded to prolactin and produced more MTV than cells cultured in tissue culture dishes. Of the three media tested, Dulbecco's modified Eagle's medium was the best in terms of responsiveness to prolactin and max MTV production. Studies with other pituitary and placental hormones showed that growth hormones and human placental lactogen could replace prolactin, whereas follicle-stimulating hormone, luteinizing hormone, and thyrotropin were ineffective. In the normal mammary epithelial cells, insulin and glucocorticoid elicited only a small increase in MTV production in the absence of prolactin. Although prolactin alone had little effect, its presence was necessary for max glucocorticoid-stimulated MTV production in normal cells. (24 refs.)

77-5755 Transmission of Mammary Tumor Virus in Mouse Strain DD: Further Support for the Uniqueness of Strain GR. (Eng) Vlahakis, G. (Gene Regulation Section, Lab. Molecular Biology, NCI, NIH, Public Health Service, U.S. Dept. Health, Education, and Welfare, Bethesda, MD 20014); Heston, W. E.; Chopra, H. C. *J Natl Cancer Inst* 59(5): 1553-1555; 1977.

The ability of DD male mice to transmit murine mammary tumor virus (MuMTV) was examined by outcrossing them to MuMTV-negative strains. Another purpose of this experiment was to determine the uniqueness of MuMTV transmission in strain GR mice. Twenty-nine of 39 females from (DD female x BALB/c male) crosses had mammary tumors. The av age at tumor appearance was 13.8 mo. Thirty-three of 44 females from (DD female x C57BL male crosses) developed mammary tumors. The av age at tumor appearance was 17.5 mo. The corresponding tumor incidence for reverse crosses, using DD males, was 2.6% and 0%, respectively. Most of the mammary tumors in the high-incidence groups were diagnosed as adenocarcinomas. The mode of vertical transmission of MuMTV in the high-incidence strain DD is by the milk, but in the similar and possibly related strain GR, MuMTV is transmitted by either parent. These findings highlight the uniqueness of strain GR mice. (15 refs.)

77-5756 Expression of Murine Mammary Tumor Virus-related Antigens in Human Breast Carcinoma (MCF-7) Cells. (Eng) Yang, N. S. (Dept. Biology, Michigan Cancer Foundation, 110 E. Warren Ave., Detroit, MI 48201); Soule, H. D.; McGrath, C. M. *J Natl Cancer Inst* 59(5): 1357-1367; 1977.

The specific expression of murine mammary tumor virus (MuMTV) cross-reactive antigens in a cultured human breast carcinoma (MCF-7) is reported. The number of specifically reactive MCF-7 cells was augmented two- to threefold by progesterone (10^{-7} or 10^{-8} M). Neither 5-Iododeoxyuridine (IUdR) nor dexamethasone alone or in combination had any effect on MuMTV cross-reactive antigen expression in MCF-7 cells. Late-passage MCF-7 monolayers were phenotypic mixtures of 80%-90% small cells (S cells) and 10%-20% large cells (L cells). The L cells reacted exclusively with MuMTV antisera and responded to progesterone with augmented antigen levels. When L cells were separated from S cells by cloning, only L cells in L cell clones reacted with MuMTV antisera. The number of L cell clones increased from 15% to 35% after prolonged treatment of the parent monolayer cells with IUdR; this resulted in a parallel increase in MuMTV-positive L cells. However, the segregation of L cells from S cells and the increase in L-cell number by IUdR treatment did not permanently increase the number of MuMTV-positive cells. MuMTV-positive L cells converted rapidly to MuMTV-negative L cells during cell division. To determine the sequence of events in the diminution of antigen synthesis in MCF-7 cell monolayers, earlier MCF-7 passages were examined. Passages 6-10 of one subline were 50%-60% positive in reactivity with anti-MuMTV sera. Approx 80% of the cells in these passages were L cells. Within four subsequent passages, the percentage of MuMTV-positive cells diminished from 50%-60% to 4%-6%. During that time, the cultures contained at least 70% L cells. Two models of growth dynamics are proposed to account for phenotypic interconversions of MCF-7 cells during the in vitro proliferation. (35 refs.)

77-5757 Type-specific Antigenic Determinants on the Major External Glycoprotein of High- and Low-oncogenic Murine Mammary Tumor Viruses. (Eng) Teramoto, Y. A. (Meloy Labs., Springfield, VA 22151); Kufe, D.; Schlom, J. *J Virol* 24(2): 525-533; 1977.

Antisera prepared against mouse mammary tumor virus (MMTV) of C3H mice and externally labeled virions of the virus were used to distinguish between the gp52's of the high-oncogenic MMTV of C3H mice [MMTV(C3H)] and the low-oncogenic MMTV of the same strain [MMTV(C3HF)]. The virions were obtained from the milk of RIII and C3H/C57BL mice and from culture fluids of primary mammary tumor cells. Comparison of the intact virion and purified gp52 radioimmunoassays showed that MMTV type-specific differences were enhanced with the intact virion radioimmunoassay. These differences were further magnified with appropriately absorbed antisera. The gp52's contained type-specific antigenic determinants. It is unlikely that the type-specific differences were due to differences in host-derived antigens or in host-coded glycosylation. The type-specific reactivities could be magnified by the use of an antisera dilution that does not give max sensitivity, use of the virion assay

instead of the purified gp52 assay, and absorption of antisera with a particular strain of MMTV. (37 refs.)

- 77-5758 Nuclear Localization of DNA Polymerase α and DNA Synthesis in Polyoma Virus Infected Mouse Cells.** (Eng) Wintersberger, U. (Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, 1090 Vienna IX, Austria); Wintersberger, E. *Oncology* 34(5): 190-192; 1977.

Studies using inhibitors of DNA synthesis showed DNA polymerase α concentrations in the nuclei of polyoma virus-infected Swiss mouse cells were high in DNA replication. These results indicated that the enzyme is actively transported into nuclei concomitant with the onset of DNA synthesis, or that it is bound much more strongly in nuclei during DNA replication. In either case, the observations support the hypothesis that DNA polymerase α is involved in the replication of cellular and viral DNA. (11 refs.)

- 77-5759 Transplacental Transmission of Polyoma Virus in Mice.** (Eng) McCance, D. J. (Dept. Microbiology, Guy's Hosp. Medical Sch., London Bridge, London SE1 9RT, England); Mims, C. A. *Infect Immun* 18(1): 196-202; 1977.

When pregnant CD-1 mice were inoculated ip on day 1 of gestation with polyoma virus, some exhibited total resorption or reduced litter size, the extent depending on the dose. Virus was detected in 4/11 mouse embryo fibroblast (MEF) cultures made from infected mothers. After maternal infection on day 5 or 10 of gestation, virus titers of up to 10^7 TCID₅₀ (50% tissue culture infectious doses) per gram of fetus were found in all pools of fetuses tested 5 days later, with the titers falling by day 6. Hemagglutination-inhibiting antibodies against polyoma appeared in maternal serum by day 6 and rose to a max by day 14. IgG antibodies were detected by day 7, with titers rising rapidly to a max at day 14. After maternal infection later in gestation (day 15), 1/3 litters of newborn mice had 10^5 TCID₅₀ of polyoma virus per gram in pooled kidney samples. (20 refs.)

- 77-5760 State of the Viral DNA in Rat Cells Transformed by Polyoma Virus. II. Identification of the Cells Containing Nonintegrated Viral DNA and the Effect of Viral Mutations.** (Eng) Zouzias, D. (Dept. Pathology, New York Univ. Sch. Medicine, New York, NY 10016); Prasad, I.; Basilico, C. *J Virol* 24(1): 142-150; 1977.

Fischer rat fibroblasts (F2408 cells) transformed by polyoma virus contained both integrated and nonintegrated viral DNA. The presence of the latter was under the control of

the *A* early viral function. Rat cells transformed by a temperature-sensitive polyoma mutant, *ts-a*, lost free viral DNA when grown at the nonpermissive temperature (40 C), but they reexpressed it 1-3 days after they were shifted back to the permissive temperature. In contrast, rat cells transformed by a late viral mutant, *ts-8*, contained free viral DNA at both temperatures. Treatment of the transformed rat cells with mitomycin C increased the quantity of free viral DNA and produced infectious virus. Experiments of in situ hybridization, with ³H-labeled polyoma complementary RNA as a probe, showed that only 0.1% of the transformed cells contained nonintegrated viral DNA at any given time. These results suggest that the presence of free viral DNA in polyoma-transformed rat cells is due to spontaneous induction of viral DNA replication, and that free viral DNA molecules originate from integrated ones, probably through excision and limited replication. (24 refs.)

- 77-5761 Analysis of Polyoma Virus DNA Replicative Intermediates by Agarose Gel Electrophoresis.** (Eng) Martin, R. F. (Biological Res. Univ., Cancer Inst., Melbourne, 3000, Australia). *J Virol* 23(3): 827-832; 1977.

Agarose gel electrophoresis was used to fractionate polyoma virus (Py) replicative intermediates (RI) according to maturity. Three peaks were identified: Py DNA (I), Py DNA (II), and a peak which corresponded to high mol wt cellular DNA which remained in spite of the extraction procedure. There was an inverse relationship between electrophoretic mobility and maturity of RI. Further analysis was complicated by the presence of both supercoiled and relaxed molecules. Separation of these components indicated that the relaxed RI were less mature than the supercoiled RI. However, the procedure could only provide relatively pure populations of mature (> 70%) relaxed RI molecules or immature (< 60%) supercoiled ones. The electrophoretic mobilities of linear and circular duplex DNA molecules were also compared. (21 refs.)

- 77-5762 Altered Virion Proteins of a Temperature-sensitive Mutant of Polyoma Virus, *ts59*.** (Eng.) Gibson, W. (Dept. Pharmacology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD 21205); Hunter, T.; Cogen, B.; Eckhart, W. *Virology* 80(1): 21-41; 1977.

Several series of experiments were performed to determine the properties of a temperature-sensitive (*ts*) mutant of polyoma virus, *ts59*, which is blocked during the late stage of infection at the restrictive temperature. Genetic analysis by complementation and marker rescue showed that *ts59* maps in the late region of the polyoma genome, between 27 and 54 map units. The marked heat lability of the infectivity and hemagglutinating ability of *ts59* virions suggests that there

may be changes in one or more of its three capsid proteins. All three (VP1, 45,000 daltons; VP2, 30,000 daltons; and VP3, 20,000 daltons) showed altered mobilities upon sodium dodecyl sulfate-polyacrylamide gel electrophoresis. In addition, the tryptic peptide patterns of these proteins differed from those of wild-type proteins. Analyses in vitro and in infected cells demonstrated that the changes in the proteins are caused by differences in primary structure rather than by posttranslational modifications. The capsid proteins of revertant virions produced by marker rescue of the ts phenotype of ts59 were analyzed. It was found that 26 map units is the furthest point that the location of the C-terminus of VP1 can be from the *Eco*.R1 cleavage site in a clockwise direction, that the N-terminal end of VP2 extends beyond that of VP3, and that the ts phenotype of ts59 corresponds with a peptide alteration common to VP2 and VP3. One of the consequences of ts59 mutation appears to be a decreased synthesis of viral capsid proteins at the restrictive temperature, apparently resulting from lower amounts of viral messenger RNA in the infected cells. (32 refs.)

- 77-5763 **Mechanisms of Gene Regulation During Stimulated Cellular Proliferation: Effects of Type C RNA Virus Expression (Meeting Abstract).** (Eng.) Benz, E. W. (Univ. Minnesota, Minneapolis, MN 55455). *Diss Abstr Int [B]* 38(3): 1172-1173; 1977. (no refs.)

- 77-5764 **Appearance of C-Type RNA Viruses During the Development of Radiation-Induced Osteosarcomas (Meeting Abstract).** (Eng.) Erfle, V. (Ges. f. Strahlen-u. Umweltforschung mbH Munchen, Munich, W. Germany); Luz, A.; Marquart, K. H.; Hehlmann, R. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 58; 1977. (no refs.)

- 77-5765 **C-Type Virus Activation During Chemical Leukemogenesis (Meeting Abstract).** (Eng.) Nexø, B. A. (Fibiger Lab., DK-2100 Copenhagen Ø, Denmark); Ulrich, K. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 54; 1977. (no refs.)

- 77-5766 **Binding of Ferritin-Lectin Conjugates to C-Type Virus in Intact Cells.** (Eng.) Manuelidis, L. (Dept. Pathology, Yale Univ. Sch. Medicine, 310 Cedar

St., New Haven, CT 06510) Tomita, M.; Manuelidis, E. E. *Experientia* 33(7): 949-952; 1977.

The binding of ferritin-lectin conjugates to C-type virus in TC509 cells (derived from a methylcholanthrene-induced mouse glioblastoma producing C-type particles) and other glioblastoma and normal lines was studied to investigate if there are restricted or clustered binding sites on the cell membrane and if the membrane of the viral bud or of the mature virus can be distinguished from the rest of the cell membrane. The plant lectins *Ricinus communis* agglutinin, specific for β -galactopyranosyl-like residues, and Concanavalin A (Con A), specific for α -D mannopyranosyl-like residues, were used. Both ferritin-Ricin and ferritin-Con A conjugates bound to all exposed surfaces of the TC509 cells and to budding as well as mature virus particles. No differences in binding between the viral coat and adjacent plasma membrane were detected. The ferritin was evenly distributed with no clustering of particles. Studies of other glioblastoma cells producing no C-type particles, including a human glioblastoma, showed similar intense binding. Lectins conjugated with ferritin appeared to retain their polyvalent character, allowing them to form a bridge between two or more virus particles producing viral aggregates. The conjugates also induced phagocytosis of viral particles by the cell, probably by linking them to the plasma membrane. Such conjugates, or lectins alone, might be useful in stimulating an increased uptake of virus. (13 refs.)

- 77-5767 **Surface Morphology and Oncornaviral Gene Expression of Normal and Neoplastic Cells (Meeting Abstract).** (Eng.) Cloyd, M. W. (Duke Univ., Durham, NC 27706). *Diss Abstr Int [B]* 38(4): 1562; 1977. (no refs.)

- 77-5768 **RNase T1-resistant Oligonucleotides of Akv-1 and Akv-2 Type C Viruses of AKR Mice.** (Eng.) Rommelaere, J. (Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA 02139); Faller, D. V.; Hopkins, N. *J Virol* 24(2): 690-694; 1977.

Electrophoresis and RNase digestion were used to determine the degree of similarity between the genomes of Akv-1 and Akv-2 viruses. Electrophoresis of labeled fingerprints of RNase T1-resistant oligonucleotides revealed identical electrophoretic patterns. Pancreatic RNase digestion appeared to produce identical products, suggesting that the RNase T1-resistant oligonucleotides of the two viruses are identical. If they are identical, the Akv-1 and Akv-2 loci may have resulted from two integrations of the same viral genetic material, possibly as the result of infection of germ line cells by an Akv virus. (8 refs.)

77-5769 Induction of Xenotropic C-type Viruses from Mouse B Lymphocytes (Meeting Abstract). (Eng.) Schumann, G. (Res. Dept., Pharmaceuticals Div., Ciba-Geigy Ltd., Basel, Switzerland); Moroni, C. *Z Immunitaetsforsch* 153(4): 352; 1977. (no refs.)

77-5770 Genetic and Functional Relationship between A-particles from Mouse Plasmacytomas and C-type Viruses (Meeting Abstract). (Eng.) Weimann, B. (Basel Inst. for Immunology, Basel, Switzerland); Schmidt, J.; Pragnell, I. B. *Z Immunitaetsforsch* 153(4): 363; 1977. (no refs.)

77-5771 Studies on Reptilian Type-C Oncornaviruses (Meeting Abstract). (Eng.) Andersen, P. R. (Univ. Delaware, Newark, DE 19711). *Diss Abstr Int [B]* 38(4): 1599-1600; 1977. (no refs.)

77-5772 Evolutionary Relationships Between *gag* Gene-coded Proteins of Murine and Primate Endogenous Type C RNA Viruses. (Eng.) Barbacid, M. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD 20014); Stephenson, J. R.; Aaronson, S. A. *Cell* 10(4): 641-648; 1977.

The low mol wt structural proteins p15, p12, and p10 of representative endogenous C-type viruses of the RD114/baboon group were compared with those of Rauscher murine leukemia viruses (MuLV). Biochemical and immunological testing of viruses following fractionation by agarose gel filtration in the presence of 6 M GuHCl demonstrated that the p10 proteins of each group are very similar. In addition, Rauscher MuLV p15 and RD114 p12 exhibited similar hydrophobic characteristics and demonstrated cross-reactive antigenic determinants. The RD114 p15 and Rauscher MuLV p12, both highly type-specific, major phosphoproteins of their respective viruses, were hydrophilic and had an extended tertiary structure, indicating a reciprocal relationship between the p12 and p15 proteins of the two groups. Along with previous evidence for the immunological relatedness of their major internal viral proteins, p30, these results demonstrate that each of the *gag* gene-coded proteins of Rauscher MuLV has an analog in the RD114 virus. A tentative model elucidates the evolution of these endogenous viruses in terms of their respective gene translational products. (35 refs.)

77-5773 Lack of Expression of Type C Hamster Virus after Neoplastic Transformation of Hamster Embryo Fibroblasts by Benzo(a)pyrene. (Eng.) Reitz, M. S. (Litton Bionetics, Inc. Bethesda, MD 20014); Saxinger, W.

C.; Ting, R. C.; Gallo, R. C.; DiPaolo, J. A. *Cancer Res* 37(10): 3585-3589; 1977.

Syrian hamster embryo fibroblasts transformed in vitro by benzo(a)pyrene were analyzed for the presence of C-type viral components, including extra- and intracellular reverse transcriptase activity, intracellular C-type hamster virus-related RNA, and cellular hamster virus group-specific antigen. No evidence could be found for any of these components, although they were easily detectable in hamster fibroblasts producing B-34 virus (a hamster virus pseudotype of Harvey murine sarcoma virus that contains an excess of helper G type hamster virus) or Harvey virus itself. In addition, intracellular viral RNA could not be detected in normal hamster embryo fibroblasts, in hamster fibroblasts transformed by simian virus 40, or in newborn hamster kidney and liver. Thus, the detectable expression of indigenous hamster G type virus is not required to maintain the transformed phenotype of these cells. (32 refs.)

77-5774 Changes in Plasma Membrane Proteins of Virus-Transformed Cells (Meeting Abstract). (Eng.) Montagnier, L. (Viral Oncology Unit, Institut Pasteur, Paris, France). In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 33; 1977. (no refs.)

77-5775 Expression of Mason-Pfizer and Simian Type C Viruses in the Presence of 5-Iododeoxyuridine and Dexamethasone. (Eng.) Ahmed, M. (John L. Smith Memorial Cancer Res., Pfizer Incorporated, Maywood, NJ 07607); Schidlovsky, G.; Harewood, K. R.; Manousos, M.; Mayyasi, S. A. *J Natl Cancer Inst* 58(5): 1515-1518; 1977.

The effect of 5-iododeoxyuridine (IUdR) and dexamethasone phosphates (DXM) on the replication and production of Mason-Pfizer monkey virus (M-PMV) was studied in CMMT cells (a M-PMV-producing cell line developed by cocultivation of a monkey mammary tumor with normal monkey embryo cells). Monolayer cultures of CMMT cells were incubated with medium supplemented with (1) DXM (2.5×10^{-5} M) for 96 hr or (2) IUdR (25 μ g/ml) for 24 hr. Treated and untreated CMMT cells were examined by indirect immunofluorescence with antisera prepared against M-PMV, baboon C-type virus (BV), and Rauscher leukemia virus (RLV). Production of infectious M-PMV was enhanced after DXM treatment. The reverse transcriptase (RT) activity and infectivity titers of treated culture fluids were enhanced 5 and 10 times, respectively. A simian C-type virus (SCV) was also detected by electron microscopy and RT analysis. The SCV was serologically related to the endogenous BV. IUdR ac-

tivated the SCV in the CMMT cell line, but significantly inhibited the production of infectious M-PMV. Removal of DXM or IUdR from the growth medium resulted in the disappearance of SCV buds and related RT activity; low levels of specific viral structural proteins, however, continued to be synthesized intracellularly. The DXM-induced enhancement of M-PMV was also lost when the treated cells were subcultured for 2 wk in the absence of the hormone. (18 refs.)

- 77-5776 **Distribution of Mason-Pfizer Virus-specific Sequences in the DNA of Primates.** (Eng.) Drohan, W. (Meloy Labs, Inc., Springfield, VA 22151); Colcher, D.; Schochetman, G.; Schlom, J. *J Virol* 23(1): 36-43; 1977.

In RNA-DNA hybridization experiments using iodinated Mason-Pfizer virus (MPV) 60S-70S RNA isolated from a normal human lymphocyte cell line (NC-37), approx 20% of the MPV genome was found to exist as endogenous provirus in rhesus monkey tissues. DNA's from normal tissues of other Old World monkeys (baboon, African green, and patas) showed similar hybridization. However, DNA's from a variety of tissues from New World monkeys and 60S-70S RNA's from M7 (endogenous virus of baboons), RD-114 (endogenous virus of cats), and simian sarcoma virus showed no homology. Results of several other experiments confirmed the fact that the MPV-specific proviral sequences are the same in rhesus, baboon, African green, and patas DNA's: (1) T_m values of all these hybrids were identical; (2) removal of MPV sequences endogenous to rhesus monkeys by recycling resulted in a loss of hybridization with the other three species; (3) C₀t_{1/2} values were approx 3,000 for all four species; and (4) mixing experiments resulted in hybridization kinetics identical to those found for the individual species. (17 refs.)

- 77-5777 **Production of Antiserum to the Reverse Transcriptase of Mason-Pfizer Monkey Virus.** (Eng.) Harewood, K. (John L. Smith Memorial Cancer Res., Pfizer Incorporated, Maywood, NJ 07607); Ahmed, M. *J Gen Virol* 36(2): 227-235; 1977.

The production of antiserum to the reverse transcriptase (RT) of Mason-Pfizer monkey virus (M-PMV) was studied. Sera from three randomly bred young adult New Zealand white rabbits immunized with the partially purified protein (0.2 mg/wk x 5) were immunologically specific for M-PMV polymerase. DNA polymerase from SSV-1 and RT from Rauscher leukemia virus and endogenous baboon C-type virus were not inhibited. Some human breast cancer tissue extracts have been shown to possess M-PMV-related antigens and nucleic acid sequences. Since the M-PMV RT antiserum specifically inhibited M-PMV polymerase and since this activity resided in the IgG fraction of the serum, these reagents may be potentially useful for identifying M-PMV-like virus

isolates and for further probing human tissues for M-PMV RT-related activities. (21 refs.)

- 77-5778 **Differential Synthesis of Mammalian Type C Viral Gene Products in Infected Cells.** (Eng.) Krakower, J. M. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD 20014); Barbacid, M.; Aaronson, S. A. *J Virol* 24(1): 1-7; 1977.

Radioimmunological techniques were used to quantitate the translational products of the *gag*, *pol*, and *env* genes to mammalian C-type viruses. Analysis of the viral proteins associated with simian sarcoma-associated virus (SSAV) and SSAV-infected cells revealed that the reverse transcriptase (RT) in the virus and infected cells was < 1% of that of the major viral structural protein, p30. The rate of intracellular degradation of RT in SSAV-infected cells was no greater than that of several viral structural proteins, indicating that the lower viral enzyme levels resulted from its decreased synthesis. By screening individual cells infected at limiting SSAV dilution it was possible to isolate a clone (clone 16), that had levels of viral p12, p30, and gp70 similar to those found in wild-type SSAV-infected cells and that released noninfectious virions in large quantity. The noninfectious virions and clone 16 cells lacked immunologically or enzymologically detectable RT. With serial passage of clone 16 cells, RT activity became spontaneously detectable in tissue culture fluids, concomitant with the appearance of infectious virus. The RT associated with this virus was indistinguishable from SSAV polymerase, indicating that the genetic alteration restricting SSAV *pol* gene expression in clone 16 cells was reversible. These results further demonstrate the strict requirement of RT for establishment of C-type virus infection. Possible mechanisms of C-type viral gene expression in SSAV-infected cells are discussed. (30 refs.)

- 77-5779 **Isolation of the Major Glycoprotein (gp70) of Simian Sarcoma Virus (SSV-1/SSAV-1) in Preparative Quantities.** (Eng.) Thiel, H. J. (Max-Planck-Institut für Virusforschung, Spemannstrasse, 35/III, D-7400 Tübingen 1, W. Germany); Bergholz, C.; Beug, H.; Deinhardt, F.; Schwarz, H.; Schafer, W. *Z Naturforsch [C]* 32(9/10): 884-886; 1977.

The major glycoprotein (gp70) of simian sarcoma virus is present in soluble form in the medium of virus-producing suspension cultures. It could be isolated in substantial amounts from the supernatant of these cultures by an immunoadsorbent technique. Some of its gel-electrophoretic and serological properties are described. (21 refs.)

- 77-5780 **Evolution of Primate Oncornaviruses: An Endogenous Virus from Langurs (*Presbytis* spp.)**

with Related Virogene Sequences in Other Old World Monkeys. (Eng) Benveniste, R. E. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD 20014); Todaro, G. J. *Proc Natl Acad Sci USA* 74(1): 4557-4561; 1977.

Gene sequences related to a retrovirus (D-type oncornavirus) isolated from a lung cell culture from the D-type spectacled langur (*Presbytis obscurus*) were found in multiple copies (20-40/haploid genome) in langur cellular DNA. Partially homologous virogene sequences were present in the DNA of related Old World monkey species. Primates thus contain gene sequences for at least two distinct classes of genetically transmitted oncornaviruses, the C-type (isolated from baboons) and the D-type. The langur virus is partially related to Mason-Pfizer monkey virus, a D-type retrovirus isolated from rhesus monkeys. Nucleic acid hybridization studies suggest that Mason-Pfizer monkey virus, now infectious among primates, was derived from an endogenous virus of langurs or from another member of the primate subfamily Colobinae. (44 refs.)

77-5781 Oncornavirus-like Particles in Squirrel Monkey (*Saimiri sciureus*) Placenta and Placenta Culture. (Eng) Smith, G. C. (Southwest Foundation Res. and Education, Post Office Box 28147, San Antonio, TX 78284); Heberling, R. L.; Helmke, R. J.; Barker, S. T.; Kalter, S. S. *J Natl Cancer Inst* 59(3): 975-979; 1977.

Oncornaviruslike particles similar in morphology to D-type particles were observed in placentas from 1/2 squirrel monkeys. Intracytoplasmic A-type particles, immature virus particles, and mature viruses with eccentric or occasionally centric nucleoids were associated with placental syncytiotrophoblasts. Surface projections of the typical B-type virus spike layer were not observed on the outer envelopes. Cultures derived from the virus-positive squirrel monkey placenta and cocultivated with a mink lung culture revealed oncornaviruses that were identical to those previously isolated in vivo and similar to Mason-Pfizer monkey virus. The major morphologic difference between the in vivo and in vitro squirrel monkey virus was in the nucleoid position of the mature virus particles. (33 refs.)

77-5782 Effect of Ethanol and Prednisolone on Growth Rate and Adherence of Normal and SV 40 Transformed Hamster Fibroblasts. (Eng) Maziere, J. C. (C.H.U. Saint-Antoine, Service de Chimie Biologique, 27, rue Chaligny, 75571 Paris Cedex 12, France); Maziere, C.; Polonovski, J. *Biomedicine [Express]* 27(6): 236-238; 1977.

Ethanol (0.5% volume/volume) or prednisolone (14.4×10^6 M) in ethanol solution was added to cultures of normal or simian virus 40-transformed hamster fibroblasts. Ethanol inhibited and prednisolone stimulated the growth of normal

cells. Neither compound affected the growth of transformed cells. The detachment and mortality of transformed cells increased in the presence of ethanol and decreased in the presence of prednisolone. The two factors had no effect on cell adherence or mortality of normal cells. (14 refs.)

77-5783 Heterogeneity of Karyotype and Growth Potential in Simian Virus 40-transformed Chinese Hamster Cell Clones. (Eng) Zuna, R. E. (Dept. Pathology, Univ. Colorado Medical Center, Denver, CO 80262); Lehman, J. M. *J Natl Cancer Inst* 58(5): 1463-1472; 1977.

Five clones of Chinese hamster cells transformed with simian virus 40 (SV40) were isolated from methylcellulose and characterized as to Giemsa-banded karyotype within 20 cell generations of infection and DNA content, saturation density, agglutination with concanavalin A (Con A) and tumorigenicity at early and late passage. There was an increase in cloning efficiency on plastic with increased passage in culture. Colony formation in methylcellulose decreased markedly with increasing passage in culture. Only 2/5 clones studied showed significant agglutination with Con A over controls. Cells from 3/5 clones produced tumors in hamsters, but only one of these lines yielded tumor cells that produced a tumor upon reinjection. Chromosome analysis and DNA content studies at early passage revealed that the genetic complement for all clones was predominantly near tetraploid. All cultures examined contained a proportion of hypertetraploid cells. Nonrandom chromosome changes included at least one broken No. 1 chromosome in 80% or more of the cells in each clone and fewer sex chromosomes than anticipated from the cell ploidy. Several abnormal marker chromosomes tended to recur. These changes were more pronounced in the cells from tumors formed by the three tumorigenic clones. A karyotypically stable stem line was not noted for any of the clones or tumors. The lack of correlation between in vivo and in vitro growth potential suggests that the cells that proliferate when a tumor is placed into culture are not exclusively (or even predominantly) the cells that are responsible for tumor growth in vivo, but are variant cells produced as a result of mitotic abnormality. (18 refs.)

77-5784 SV40-3T3 Cell Plasminogen Activator-mediated Initiation of Mitosis in Quiescent 3T3 Cells (Meeting Abstract). (Eng) Whur, P. (Marie Curie Foundation, Oxted, Surrey, England); Gordon, M.; Williams, D. C.; Urquhart, C.; Wright, E. *Br J Cancer* 36(3): 402; 1977. (1 ref.)

77-5785 Regulation of Early and Late Simian Virus 40 Transcription: Overproduction of Early Viral

RNA in the Absence of a Functional T-Antigen. (Eng.) Khoury, G. (Lab. DNA Tumor Viruses, NCI, Bethesda, MD 20014); May, E. *J Virol* 23(1): 167-176; 1977.

African green monkey kidney cells infected with either wild type simian virus 40 (SV40) or an early SV40 temperature-sensitive mutant (tsA58) were grown at various temperatures (31.5-41 C) and harvested 48 hr later. Filter hybridization determinations indicated that infected cells synthesized 4.5%-8.0% virus-specific RNA, of which 5%-10% was early SV40 RNA. From 31.5 to 37 C, tsA58-infected cells produced 5.2%-8.0% virus-specific RNA; in the absence of DNA replication at 41 C, however, only 0.4% was produced. In these cells, the ratio of early to total SV40 RNA reflected an absolute overproduction of early SV40 RNA (and a consequent underproduction of late SV40 RNA) that increased with temperature. In experiments in which tsA58-infected cells were incubated at 32 C and shifted to 40 C at 48 hr postinfection, the ratio of early to total increased from 0.25 to between 0.6 and 0.7 24 hr after the shift. Analogous experiments using sarkosyl-extracted viral transcriptional complexes yielded similar results, indicating that overproduction occurred at the level of transcription. Results of the treatment of infected cultures with cytosine arabinoside (40 µg/ml) for 2-6 hr suggest that overproduction may be associated with a functional defect in the tsA58 T antigen that results from thermal inactivation. (28 refs.)

77-5786 An Analysis by Electron Microscopy of Early Simian Virus 40 RNA from a tsA Mutant. (Eng.) Reed, S. I. (Dept. Genetics, Univ. Washington, Seattle, WA 98195); Alwine, J. C. *Cell* 11(3): 523-531; 1977.

Early simian virus 40 (SV40) RNA from a temperature-sensitive mutant (tsA) was analyzed by a new electron microscopy technique. The technique involves initial hybridization of RNA with restriction endonuclease (Eco RI)-treated SV40 DNA, followed by reaction of single-stranded DNA with DNA binding protein and monovalent antibodies to this protein. The termini of the RNA were found in a nonrandom distribution, with the largest number of RNA end points between 0.30 and 0.42 SV40 fractional length from the nearer end of full-length Eco RI linear SV40 E-strand DNA. A large proportion (44%) of the heteroduplex molecules had a duplex region extending to one end. Orientation of the hybridized RNA was achieved by the use of an SV40 deletion mutant (dIE 1228). The mean 5' terminus of early nuclear SV40 RNA was at 0.68 SV40 fractional length, with the 5' termini mapping at a distinct peak between 0.60 and 0.74 SV40 fractional length. The nuclear 3' termini mapped over a broad peak between 0.72 and 0.50 SV40 fractional length, indicating an abundant class of small RNA molecules with sizes between 0.01 and 0.20 SV40 fractional length. In addition, a large class of RNA molecules with a 3' terminus at the end of the E strand were present. These results suggest that the promoter for early transcription is at or near map position 0.67. (22 refs.)

77-5787 The SV40 DNA Template for Transcription of Late mRNA in Viral Nucleoprotein Complexes. (Eng.) Birkenmeier, E. H. (Lab. Biology Viruses, Natl. Inst. Allergy and Infectious Diseases, Bethesda, MD 20014); Radonovich, M. F.; Shani, M.; Salzman, N. P. *Cell* 11(3): 495-504; 1977.

Isolated stable RNA-DNA hybrid molecules derived from simian virus 40 (SV40) transcriptional intermediates by RNase treatment were characterized. Sedimentation analysis of the RNA-DNA hybrids in sucrose gradients containing ethidium bromide indicated that these molecules are covalently closed circular DNA molecules with negative superhelical turns similar to SV40 DNA 1, but with fewer superhelical turns due to the presence of RNA hydrogen-bonded to the DNA. The size of the ribonuclease-resistant RNA ranged from 35 to 200 bases, with most of the RNA being between 60 and 150 nucleotides; the predominant size class was 90 nucleotides. It was concluded that SV40 DNA 1 is the template for late messenger RNA transcription, although only a small fraction of viral DNA is in the transcriptional complexes. (32 refs.)

77-5788 Characterization of a Polypeptide Immunologically Related to Insulin, Synthesized by SV40-transformed Rat β Cells (Meeting Abstract). (Eng.) Niesor, E. (Institut de Biochemie Clinique, Universite de Geneve, Geneva, Switzerland); Renold, A. E.; Weil, R. *Diabetologia* 13(4): 421-422; 1977. (no refs.)

77-5789 Studies on Viral DNA-Protein Complexes Isolated at Different Times after Infection of Monkey Kidney Cells with Simian Virus 40. (Eng.) Tan, K. B. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA 19104); Howe, C. C. *Biochim Biophys Acta* 478(1): 99-108; 1977.

Viral DNA complexes were isolated from African green monkey kidney cells at intervals from 24 to > 60 hr after infection of the cells with simian virus 40. The major protein components of the DNA complexes were the viral structural polypeptide VP1 and cellular histones. At 24 hr after infection, VP1 was present in large amounts relative to histones, but at (48 hr), the complexes contained mostly histones. The amount of VP1 in a complex correlated with the amount of free VP1 present in the cells, ie VP1 not yet incorporated into virus particles. At 24 hr, about 40% of VP1 was free VP1; at 48 hr, most of the VP1 was incorporated into virus particles. In contrast, viral DNA was produced in excess and only about 13% was incorporated into virions. In agreement with this result, only 16% of the DNA in the DNA complexes could be chased into virions. There is, apparently, no turnover of newly synthesized VP1 that is associated with the DNA complex late after infection. (19 refs.)

7-5790 **The Early Region of SV40 DNA May Have More than One Gene.** (Eng) Thimmappaya, B. Dept. Human Genetics, Yale Univ. Sch. Medicine, New Haven, CT 06510; Weissman, S. M. *Cell* 11(4): 837-843; 1977.

The nucleotide sequence of 70 base pairs around the Alu I and B junctions of the genome from a single Eco RI cleavage site within simian virus 40 (SV40) DNA was determined. The messenger RNA that is transcribed from the early strand template in this stretch of DNA contains two copies of the termination codon UAA in each of the three reading frames. Thus, at least 25% of the early region of SV40 DNA does not code for the SV40 A protein, and the viral contribution to events both in the lytic cycle and in transformation may be more complex than is generally suspected. (32 refs.)

7-5791 **In Vitro Synthesis of Simian Virus 40 DNA. III. Preliminary Characterization of the Active Components in the System.** (Eng.) Cajean, C. (Unite de Physiologie des Virus, Institut de Recherches Scientifiques sur le Cancer, B. P. No. 8, 94800 Villejuif, France); Marty, J.; Suarez, F.; Girard, M. *Biochimie* 59(4): 393-402; 1977.

The in vitro synthesis of simian virus 40 (SV40) DNA was studied using cell-free, DNA-free, soluble extracts from SV40-infected CV, monkey cells. The cytoplasmic extracts were chromatographed on a diethylaminoethyl cellulose column at pH 7.5. Upon chromatography, the active extracts were resolved into two fractions. Fraction A, which was excluded from the column, contained most of the endonucleases of the cell extract but only little DNA polymerase activity. The other (fractions C + D), which eluted from the column with 200-400 mM KCl, contained the most of the DNA polymerase activity of the cytoplasmic extract but little endonuclease activity. From the known chromatographic behavior of the DNA polymerases of animal cells, the DNA polymerase in fraction A was identified as DNA polymerase β and that in fractions C + D as DNA polymerase α . The DNA polymerase that was active in the repair synthesis of SV40 DNA in vitro appeared to be DNA polymerase β . It was concluded that the in vitro repair synthesis of SV40 DNA by cytoplasmic extracts is based on the balanced activities of the endonucleases and of DNA polymerase β (recovered in fraction A), and of cell DNA ligase (recovered in fractions C + D). DNA polymerase α was inactive in the reaction. There was no significant difference between extracts from SV40-infected cells and those from uninfected cells in the amount and chromatographic properties of the enzymes examined. The results do not support the existence of an intracellular virus-specific endonuclease, at least during the early stages of the virus cycle. (38 refs.)

7-5792 **Transformation of Human Cystinotic Fibroblasts by SV40: Characteristics of Transformed Cells with Limited and Unlimited Growth Potential.** (Eng)

Oshima, R. G. (Dept. Pediatrics, Univ. California, San Diego Sch. Medicine, La Jolla, CA. 92093); Pellett, O. L.; Robb, J. A.; Schneider, J. A. *J Cell Physiol* 93(1): 129-136; 1977.

Skin fibroblasts from patients with nephropathic cystinosis were transformed with simian virus 40 (SV40) virions, cloned, and permitted to enter the degenerative (crisis) growth stage characteristic of SV40-transformed human cells. Nephropathic cystinosis is an autosomal recessively inherited metabolic disorder resulting in the intracellular accumulation of cystine. A transformed cystinotic cell line that was recovered from the crisis stage was indistinguishable from its transformed precrisis parental cell strain in growth rate in media containing 1% or 10% serum; cloning efficiency on plastic, in semisolid media, or on confluent monolayers of normal skin fibroblasts; expression of SV40 T antigen; or virus production. However, the modal DNA content of the recovered postcrisis transformed cystinotic cell line differed from that of the cloned parental precrisis transformed cell strain, suggesting that the postcrisis line was derived from a small subpopulation of the precrisis strain. The DNA content of the established cystinotic cell line continued to be unstable during subsequent subculturing, and the cells gave rise to subclones with both more and less DNA per cell. This line now has an apparently infinite growth potential and retains the hallmark of the cystinotic parental line--the storage of abnormally large amounts of intracellular nonprotein cystine. (27 refs.)

77-5793 **Resistance of Teratocarcinoma Stem Cells to Infection with Simian Virus 40: Early Events.** (Eng) Swartzendruber, D. E. (Los Alamos Scientific Lab., Univ. California, Ten Site H-6, Los Alamos, NM 87544); Friedrich, T. D.; Lehman, J. M. *J Cell Physiol* 93(1): 25-30; 1977.

Multipotential stem cells of a murine teratocarcinoma are resistant to typical infection with polyoma virus (PV) or simian virus 40 (SV40). Differentiated progeny of the stem cells are susceptible to infection in a manner identical to other mouse somatic cells, ie, they are permissive for PV and nonpermissive for SV40. The early interactions between the stem cells (embryonal carcinoma or EC cells) and SV40 and PV were studied. Virions adsorbed to and penetrated into the cytoplasm and nucleus of EC cells, but did not induce the expression of T antigen in the EC nuclei. Purified SV40 DNA was capable of inducing T antigen in differentiated teratocarcinoma cells but not in EC cells. Virus could not be rescued from EC cells previously exposed to SV40. The resistance of the stem cells to infection apparently involves a block in the infectious cycle after adsorption and penetration but before T-antigen induction. (21 refs.)

77-5794 **In Vivo and In Vitro TSTA-inducing Activity of Temperature-sensitive (ts) Mutants of SV40.**

(Eng) Deichman, G. I. (Lab. Tumor Immunology, Cancer Res. Center, Acad. Medical Sciences, Moscow, USSR); Kluchareva, T. E.; Kashkina, L. M. *Int J Cancer* 20(4): 616-623; 1977.

In vivo tumor-specific transplantation antigen (TSTA) induction in Syrian hamsters was studied with the use of simian virus 40 (SV40) temperature-sensitive (ts) mutants (A, B, C, BC, and D). The ts A30, A239, and, possibly, BC210 mutants were defective in resistance-inducing activity in hamsters, in contrast to wild-type SV40 and other ts mutants. At the permissive temperature, A30 and A239 did not induce TSTA in hamster cells during abortive infection in vitro, but they did so in green monkey cells at both permissive and nonpermissive temperatures. In hamster cells transformed by the A30, A239, and A209 mutants, no TSTA or very little antigen was detected by in vivo transplantation immunologic tests. Thus, expression of TSTA induced by these three SV40 ts A mutants is dependent on the species of cells infected and is a temperature-independent viral function. (24 refs.)

77-5795 **Decline in Mutation Frequency in Temperature-sensitive SV40 Viruses Before Viral DNA Synthesis.** (Eng) Cleaver, J. E. (Lab. Radiobiology, Univ. California, San Francisco, CA 94143). *Mutat Res* 44(3): 291-298; 1977.

Lesions that promote reversion from a temperature sensitive (ts) to a wild-type phenotype were induced in ts late mutants of simian virus 40 (SV40) by UV irradiation. When cultures of CV1 monkey cells infected with UV-irradiated ts mutants were grown at the permissive temperature (32 C) and then at the restrictive temperature (39 C), the reversion frequency declined just before the onset of semiconservative DNA synthesis when DNA synthesis began at 32 C. The most likely explanation for this decline is that there is competition between reactions that lead to the onset of viral DNA synthesis and reactions that repair the lesions before the onset of viral DNA synthesis. (13 refs.)

77-5796 **Mutagenesis by Simian Virus 40. II. Changes in Substrate Affinities in Mutant Hypoxanthine-Guanine Phosphoribosyl Transferase Enzymes at Different pH Values.** (Eng) Theile, M. (Acad. Sciences GDR, Central Inst. Molecular Biology, Div. Bioregulation, Dept. Cell Genetics Berlin-Buch, E. Germany); Strauss, M. *Mutat Res* 45(1): 111-123; 1977.

Several 8-azaguanine-resistant clones selected from simian virus 40 (SV40)-infected Chinese hamster cells were examined for changes in the functional properties of their hypoxanthine-guanine phosphoribosyltransferase (HGPRT). All resistant clones tested showed reduced but detectable levels of HGPRT activity. The extent of the reduction was not

identical for different substrates. In all the clones tested, including spontaneous mutants, the pH optimum for the enzymic reaction with guanine was shifted to lower values. The reduced HGPRT activities of the resistant clones correlated with their colony-forming ability in corresponding selective media. The results support the suggestion that SV40 can induce gene mutations. (25 refs.)

77-5797 **Ultrastructural Studies of H-1 Parvovirus Replication. IV. Crystal Development and Structure with the Temperature-sensitive Mutant ts1.** (Eng) Singer, I. I. (Inst. Medical Res., Putnam Memorial Hosp., Bennington, VT 05201); Rhode, S. L. *J Virol* 24(1): 343-352; 1977.

The immunocytochemistry of ts1, a temperature-sensitive mutant of H-1 parvovirus, was studied during infection of simian virus 40-transformed newborn human kidney cells. Cells fixed after 12 hr of infection showed no ts1 virions in association with euchromatin fibers. Furthermore, vacuolated nucleolar fibrous centers in ts1-infected cells grown at the restrictive temperature often contained aggregates of empty virions. By 20 to 24 hr postinfection, however, nuclei with many viral crystals that apparently developed from these aggregates of the H-1 particles were noted. Sections of the crystal exhibited three regular patterns: rodlike, hexagonal, and cubic; the basic cell unit was cubic, consisted of 16 empty particles, and measured 50 nanometers on each side. Full particles made at the permissive temperature were never observed under restrictive conditions. Various degrees of crystal dissociation were noted in cells subjected to a short temperature shift-down. Full virions were not incorporated into the crystals when cultures were shifted to the restrictive temperature. Cells containing polycrystals demonstrated a more severe cytopathology than cells with noncrystalline aggregates. The role of cellular functions in the assembly and dissociation of these crystals is discussed. (13 refs.)

77-5798 **Ultrastructural Studies of H-1 Parvovirus Replication. V. Immunocytochemical Demonstration of Separate Chromatin-associated and Inclusion-associated Antigens.** (Eng) Singer, I. I. (Inst. Medical Res., Putnam Memorial Hosp., Bennington, VT 05201); Rhode, S. L. *J Virol* 24(1): 353-362; 1977.

The immunocytochemistry of five H-1 temperature-sensitive (ts) mutants, ts1, -2, -7, -8, and -10, was studied in infected simian-virus 40-transformed newborn human kidney cells. Three separate groups of mutants were noted on the basis of their capsids at the restricted temperature. Class 1 (ts2 mutants) did not assemble capsids but produced spherical and irregular amorphous inclusions. Class 2 (ts1 and ts7) synthesized only empty particles that all aggregated and crystallized. In class 3 (ts8 and ts10), aggregates of empty virions

ere formed, but many full and empty capsids were associated with euchromatin. Synthesis of progeny DNA and hemagglutinin at the restricted temperature was normal for class mutants but defective for the other two. The data suggest the existence of two types of H-1 capsid antigens: a thermolabile inclusion-associated antigen and a thermostable chromatin-associated antigen. The former are found in proteins of assembled empty capsids that compose H-1 inclusions, and the latter are present in proteins that have not formed capsids and are concentrated on heterochromatin and nucleolar-associated chromatin. (20 refs.)

7-5799 **Physical and Genetic Characterization of Deletion Mutants of Simian Virus 40 Constructed In Vitro.** (Eng) Cole, C. N. (Dept. Human Genetics, Yale Univ. Sch. of Medicine, New Haven, CT 06510); Landers, T.; Goff, P.; Manteuil-Brutlag, S.; Berg, P. *J Virol* 24(1): 277-294; 1977.

Simian virus 40 (SV40) mutants were formed by cleavage with *Hae* II, *Bam* HI, or *Hae* III endonuclease or S1 nuclease. Ten mutants with deletions at location 0.83 were isolated as a new complementation group, E. These mutants grew slowly, without helper virus, and caused alterations in the VP2 protein only. Two mutants with deletions in the region 0.92 to 0.945 affected both VP2 and VP3; this indicates that VP3 shares sequences with the C-terminal portion of VP2. A mutant at 0.93 was the first deletion mutant of complementation group D, and it was also temperature-sensitive. Three mutants with deletions at 0/0.1 and 11 with deletions at 0.15 were in the B/C complementation group; 6 additional mutants in this group were viable, but they grew more slowly than wild type. VP1 was the only protein affected by mutants in this group. A mutant with a deletion in the region 0.72 to 0.80 exhibited a polar effect by not expressing E, D, and C genes. Mutants with deletions at 0.66 to 0.59, 0.48, 0.47, 0.33, and 0.285 to 0.205 were members of complementation group A. These mutants failed to complement each other and thus constitute a single genetic function. Two separate regions, 0.66 to 0.59 and 0.54 to 0.21, were essential for A gene function. Therefore, the A gene is the only one in the early region whose expression is necessary for productive infection in permissive cells. Approximate map locations of the SV40 genes and models for their regulation are presented. (56 refs.)

7-5800 **Structure and Formation of Circular Dimers of Simian Virus 40 DNA.** (Eng) Goff, S. P. (Dept. Biochemistry, Stanford Univ. Medical Center, Stanford, CA 94305); Berg, P. *J Virol* 24(1): 295-302; 1977.

Electron microscopy was used to determine whether covalently closed circular dimers of simian virus 40 (SV40) DNA are formed during replication or by recombinational processes and to determine whether circular dimers are precursors of

recombinant or defective viral genomes. African green monkey kidney cells were infected with 10 plaque forming units/cell of SV40; viral replication was initiated at about 14 hr, and infected cells were isolated 40 to 60 hr after infection. Heteroduplex molecules from circular dimer DNA and *Eco* RI endonuclease-generated linear *dl*-814 DNA had characteristic sets of deletion and duplication loops. A head-to-tail arrangement of the two monomeric units was demonstrated. These monomeric units were not defective, i.e., they lacked deletions or other rearrangements. Following infections with dimer DNA, nondefective monomers were formed. Upon viral infections with two distinguishable viral genomes, 95% of the dimers formed were homodimers, but about 5% were heterodimers that arose by intermolecular recombination. (17 refs.)

77-5801 **Interaction of Simian Virus 40 Chromatin with Simian Virus 40 T-Antigen.** (Eng) Persico-DiLauro, M. (Lab. Molecular Biology, Natl. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD 20014); Martin, R. G.; Livingston, D. M. *J Virol* 24(2): 451-460; 1977.

The protected regions of the simian virus 40 (SV40) genome were examined, and the binding of the tumor antigen (T antigen) to chromatin was investigated. There is a random distribution of the protected regions in SV40 chromatin, both in the absence and presence of SV40 T antigen. A modified filter binding assay was used to study T-antigen binding. Only 20% to 35% of the SV40 chromatin bound to the filters. Two to three times as much T antigen was required to bind chromatin as to bind an equivalent amount of free DNA. When the antigen concentration was fixed and DNA or chromatin was present in excess, only one-third as much chromatin as DNA was required. When antigen was present in excess, both chromatin and free DNA were quantitatively retained on the filters. It is suggested that T antigen-chromatin complexes may be formed by the binding of T antigen to chromatin and that T antigen-DNA complexes are formed by bimolecular interactions. The cooperation in chromatin binding could involve several antigen molecules and the displacement of histones. (36 refs.)

77-5802 **Evidence for Simian Virus 40 (SV40) Coding of SV40 T-Antigen and the SV40-specific Proteins in HeLa Cells Infected with Nondefective Adenovirus Type 2-SV40 Hybrid Viruses.** (Eng) Mann, K. (Dept. Mathematics and Science, Univ. Alaska, Anchorage, AK 99504); Hunter, T.; Walter, G.; Linke, H. *J Virol* 24(1): 151-169; 1977.

HeLa cells infected with nondefective adenovirus 2 (Ad2)-simian virus 40 (SV40) hybrid viruses (Ad2+ND1, Ad2+ND2, Ad2+ND4, and Ad2+ND5) synthesized SV40-specific proteins ranging from 28,000 to 100,000 daltons.

Analysis of their methionine-containing tryptic peptides demonstrated that the proteins shared common amino acid sequences. Most of the tryptic peptides derived from the smaller proteins were contained within the larger proteins. Seventeen of the 21 methionine-containing tryptic peptides of the largest SV40-specific protein (100,000 daltons) from Ad2+ND4-infected cells were identical to methionine-containing peptides of SV40 T antigen immunoprecipitated from extracts of SV40-infected cells. All of the tryptic peptides of the Ad2+ND4 100,000-dalton protein were found in SV40 T antigen immunoprecipitated from SV40-transformed cells. All SV40-specific proteins observed in vivo could be synthesized in vitro using the wheat germ cell-free system and SV40-specific RNA from hybrid virus-infected cells purified by hybridization to SV40 DNA. The in vitro products had methionine-containing tryptic peptides identical to those of their in vivo counterparts. Based on the extensive overlap in amino acid sequence between the SV40-infected and -transformed cells, it is concluded that the major portion of the SV40-specific proteins cannot be Ad2-coded. The in vitro synthesis experiments with SV40-selected RNA suggest that the SV40-specific proteins must be SV40-coded and not host-coded. Since SV40 T antigen is related to the SV40-specific proteins, it must also be SV40-coded. (62 refs.)

77-5803 Character of the Tumors Developing in Young Hamsters by the Mixed Cell Transplantation of PARA-Adenovirus 12 and SV40 Tumors--The Similarity to the Tumors Induced by PARA-Adenovirus 7. (Eng.) Chino, F. (Dept. Pathology, Natl. Inst. Health, Musashimurayama, Tokyo 190-12, Japan). *Acta Pathol Jpn* 27(3): 321-329; 1977.

The tumors that developed from the mixed cell transplantation of equal numbers (1×10^7 cells) of (1) PARA-adenovirus 12 (Ad12) tumor cells and simian virus 40 (SV40) tumor cells or (2) Ad12 and SV40 tumor cells are described and compared with tumors induced by PARA-Ad7. Syrian hamsters were inoculated sc at the age of 4 wk with 2 ml of each mixture in the interscapular and lumbar regions. All five animals in Group 1 developed tumors at both sites: 7/10 tumors were mixed, but the remaining 3 tumors and all 10 tumors induced in Group 2 were solely the SV40 type. The survival time of the Group 2 animals was 17-20 days; that of Group 1 animals was 20-30 days, indicating the greater malignancy of Ad12. In the mixed tumors, the Ad-type tumor could be distinguished clearly from the SV40-type tumor. The former was characteristic of undifferentiated tumors, composed of dense round or spindle-shaped cells, and the latter was characteristic of fibrosarcoma. The mixed tumors were morphologically identical with those induced by PARA-adeno 7, both macro- and microscopically, including the reticular fiber pattern. The results suggest that the existence of SV40 genetic information in Ad-type tumor cells is indispensable to the formation of mixed tumors in allogeneic tumor cell systems. (20 refs.)

77-5804 A Novel Method to Map Transcripts: Evidence for Homology Between an Adenovirus mRNA and Discrete Multiple Regions of the Viral Genome. (Eng) Dunn, A. R. (Cold Spring Harbor Lab., Cold Spring Harbor, NY 11724); Hassell, J. A. *Cell* 12(1): 23-26; 1977.

A method was developed for the mapping of RNA transcripts by a two-step hybridization procedure (sandwich hybridization). RNA extracted from cells infected with an adenovirus-simian virus 40 (SV40) hybrid (Ad2+ND1) was hybridized to restriction endonuclease fragments of adenovirus type 2 (Ad2) DNA immobilized on nitrocellulose filters. RNA's containing both Ad2 and SV40 sequences formed duplexes through their Ad2 sequences, leaving their SV40 sequences as protruding tails. Annealing with 32 P-labeled SV40 DNA caused these tails to become labeled, permitting autoradiographic identification of the sequences of Ad2 DNA that are homologous to the RNA. The high sensitivity of this technique, achieved through the use of 32 P-labeled RNA of high specific activity, demonstrated that hybridization of Ad2+ND1 RNA occurs at several locations on the Ad2 genome, in addition to the expected hybridization sites proximal to the SV40 insertion. (59 refs.)

77-5805 Simian Virus 40-specific Ribosome-binding Proteins Induced by a Nondefective Adenovirus 2-Simian Virus 40 Hybrid. (Eng) Jay, G. (Pediatric Oncology Branch, NCI, NIH, Bethesda, MD 20014); Jay, F. T.; Friedman, R. M.; Levine, A. S. *J Virol* 23(3): 692-699; 1977.

Human KB cells were infected with a purified, nondefective, adenovirus 2-simian virus 40 (SV40) hybrid (Ad2+ND₂), which inhibits host protein synthesis, to study the intracellular distribution of SV40-specific proteins. In addition to all of the Ad2-specific polypeptides, two new proteins with apparent mol wts of 56,000 (56K) and 42K (when analyzed on a 12.5% gel) were synthesized. Infected cells were pulse-labeled with 35 S-methionine for 20 min at 24 hr postinfection. Nuclear, cytoplasmic, and plasma membrane fractions were isolated. About 65% of the 56K protein was localized in the plasma membrane and 15% was found free in the cytoplasm. In contrast, only about 35% of the 42K was free in the cytoplasm. About 20% of each was present in the cytoplasmic fraction in a complexed form, a major portion of which was quantitatively associated with the 40S ribosomal subunits and could not be removed by 0.5 M KCl. Free, 35 S-labeled 56K and 42K cytoplasmic proteins could also bind to purified unlabeled 40S subunits in vitro. These proteins may function directly as translational control elements in cells. (32 refs.)

77-5806 Relationship Between the Methionine Tryptic Peptides of Simian Virus 40 and BK Virus Tu-

Antigens. (Eng) Simmons, D. T. (Lab. Biology Viruses, Natl. Inst. Allergy and Infectious Diseases Bethesda, MD 20814); Takemoto, K. K.; Martin, M. A. *J Virol* 24(1): 319-325; 1977.

The sizes and compositions of BK virus (BKV) and simian virus 40 (SV40) tumor antigens (T Ag) were determined. BKV was isolated from human embryonic kidney cells and SV40 from African green monkey kidney cells. BKV and SV40 T Ag's isolated from lytically infected cells had mol wts corresponding to 100,000 daltons. The chromatographic profiles of these antigens are presented. However, the monomer form of BKV T Ag from BKV-transformed cells had a mol wt of approx 113,000 daltons. The BKV and SV40 T Ag's from productively infected cells were compared by examining their methionine-labeled tryptic peptides. There were 7 pairs of similar peptides out of 20 SV40- and 21 BKV-specific peptides. These coeluting peptides contained 25% to 30% of the total methionine radioactivity. Similar results were obtained when the tryptic peptides of SV40 T Ag from lytically infected cells were compared with BKV T Ag from virally transformed cells. (20 refs.)

5807 Interspecies-, Species- and Type-specific T Antigenic Determinants of Human Papovaviruses (JC and BK) and of Simian Virus 40. (Eng) Beth, E. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Cikes, M.; Schloen, L.; Di Mayorca, G.; Giraldo, G. *J Cancer* 20(4): 551-559; 1977.

Immunofluorescence tests, absorption studies, and quantitative analysis by a sensitive ^{51}Cr microcomplement fixation (MCF) technique were used to define the degree of relatedness among the tumor (T) antigens induced by human papovaviruses, strain JC and BK, simian virus 40 (SV40), and mouse polyoma virus (PyV). Antisera against JCV, BKV, SV40 and PyV T were raised in tumor-bearing hamsters. The serologic results indicate that the T antigens of JCV, BKV, and SV40 possess various subspecificities that can be distinguished as interspecies-, species-, and type-specific antigenic determinants. JCV T and BKV T synthesized in transformed hamster cells shared the same amount (20%) of interspecies cross-reacting antigen with SV40 T from H-50 cell extracts (transformed hamster cells). Although hamster cells transformed by PyV showed definite PyV T reactivity, no cross-reactivity was found with human papovavirus and SV40 T antigens. Furthermore, a degree of heterogeneity was observed among T antigen, derived from different SV40-transformed cells. (10 refs.)

5808 Susceptibility of Common Marmosets (*Callithrix jacchus*) to Oncogenic and Attenuated Strains of *Herpesvirus saimiri*. (Eng) Wright, J. (Dept. Microbiology, Rush-Presbyterian-St. Luke's Medical Center,

1753 W. Congress Parkway, Chicago, IL 60612); Falk, L. A.; Wolfe, L. G.; Ogden, J.; Deinhardt, F. *J Natl Cancer Inst* 59(5): 1475-1478; 1977.

Common marmosets (*Callithrix jacchus*) were experimentally infected with two oncogenic strains (P-HVS and HVS-II) and one attenuated strain (A-HVS-II) of *Herpesvirus saimiri* (HVS). Inoculations with P-HVS and HVS-II led to the development of fatal lymphoproliferative disease within 23-25 days postinoculation (PI). Macroscopic and microscopic lesions induced in common marmosets by HVS-II or P-HVS were indistinguishable from those induced by HVS in cotton-topped (CT) or white lipped (WL) marmosets. The microscopic lesions in lymphoid tissues were compatible with diffuse poorly differentiated lymphoma. Lymphoblastic infiltrates were widely disseminated throughout the tissues. Virus could be isolated at 13-15 days and also at 20-21 days PI and from spleen, thymus, and lymph node necropsy tissue. Approx 85% of the cells isolated from the lymphoid tumor tissue possessed properties of T lymphocytes; < 5% expressed B-lymphocyte markers. Inoculation with A-HVS-II led to a transient inguinal lymphadenopathy 14-31 days PI, but the attenuated virus failed to produce a generalized lymphoproliferative disease and the animals survived > 1 yr with persistent HVS infections. (22 refs.)

77-5809 Observations on the Antigenic Relationships Between Epstein-Barr Virus and Herpesvirus Saimiri. (Eng) Morgan, D. G. (Dept. Pathology, Univ. Bristol Medical Sch., Univ. Walk, Bristol, BS8 1TD, England). *J Gen Virol* 36(2): 281-287; 1977.

Comparative immunofluorescence, microimmunodiffusion, and serum neutralization tests were performed to investigate antigenic relationships between Epstein-Barr virus (EBV) and herpesvirus saimiri (HVS). Complete extracts of either HVS-infected owl monkey kidney (OMK) cells (10^9) or EBV-carrying P3HR-I lymphoid cells (3×10^9) were used as antigens. Positive fluorescence occurred only when EBV-containing lymphoblasts or HVS-infected OMK cells were tested with homologous antiserum to viral capsid antigens. A potent HVS-neutralizing antiserum failed to inhibit EBV-induced transformation of cultured cord blood WBC. These results indicate that no similarities exist between the capsid or the membrane antigens of the two viruses. Microimmunodiffusion tests showed the presence of a common antigen in both extracts that is probably a nonstructural, virus-determined antigen. In view of the ability of HVS to produce a fatal lymphoma in subhuman primates, the use of this model system to study a possible relationship between EBV and malignancy is suggested. (27 refs.)

77-5810 Antibody Activity Against Antigens of Simian C-type Oncornaviruses in Serum of Melanoma

Patients (Meeting Abstract). (Ger.) Kurth, R. (Friedrich-Miescher-Lab., Tübingen, W. Germany); Huesgen, A.; Riethmüller, G.; Saal, J. G.; Thiel, J.; Schäfer, W. *Z Immunitätsforsch* 153(4): 326; 1977. (1 ref.)

77-5811 Cell Generation and Type C Virus Expression in the Human Embryonic Cell Strain HEL-12. (Eng.) Panem, S. (Dept. Pathology, Div. Biological Sciences, Univ. Chicago, Chicago, IL 60637); Prochownik, E. V.; Knish, W. M.; Kirsten, W. H. *J Gen Virol* 35(3): 487-495; 1977.

The time course of C-type virion expression was determined in serial cultures of human embryonic lung fibroblastlike cells (HEL-12) grown from frozen cell stocks. Antigen expression was determined by indirect immunofluorescence with antisera to disrupted simian sarcoma virus (SiSV) and the 28,000-molecular wt internal antigen of the endogenous cat virus RD-114/CCC. Virus production kinetics were examined by reverse transcriptase assays of culture fluids. Antigen expression and particle production could not be demonstrated during the first 20-25 days after HEL-12 cultures were reinstated in culture. An intermediate antigen-positive interval extended from 20-25 to 80 days. Cytoplasmic antigen(s) cross-reactive with an antiserum to SiSV were detected first, followed by expression of antigen(s) related to the RD-114/CCC group of C-type viruses. Extracellular C-type virus could not be demonstrated during this interval. An antigen-positive, virus-productive period extended from 80 to 120 days, but during the final interval of 120-180 days, only cytoplasmic antigens could be detected before the cells ceased growing and died. HEL-12 virus productively infected lines of human, rhesus monkey, dog, and rabbit cells. Two antigenically distinct components could be recognized with antisera to SiSV and RD-114/CCC virus by a single passage of HEL-12 virus through heterologous cells. This suggests that HEL-12 virus contains two major antigenic components. (25 refs.)

77-5812 Activation of an Endogenous C-Type RNA Virus in Rat Embryo Cells after Transformation by Herpes Simplex Virus Types 1 and 2. (Eng.) Flugel, R. M. (Inst. Virus Res., German Cancer Res. Centre, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany); Darai, G.; Braun, R.; Munk, K. *J Gen Virol* 36(2): 365-369; 1977.

Single Sprague-Dawley rat embryo cells were transformed with herpes simplex virus (HSV) type 1 or 2 at either a supraoptimal incubation temperature of 42 C or a suboptimal temperature of 20 C. Using the synthetic polymer poly rA-oligo dT as exogenous template/primer, concentrated cell culture fluids were tested individually for C-type virus DNA

polymerase activity. This activity was very low in cells transformed at 42 C compared with that found in cells transformed at 20 C. After phenol extraction and 5%-20% sucrose gradient centrifugation, ³H-uridine-labeled 70S virus RNA could be isolated from cells showing reverse transcriptase activity. At passages higher than 24, syncytia could be observed in several transformed clones. HSV transformation may activate at least part of the C-type RNA genome, but the activation does not always occur. Regardless of incubation temperature or HSV type, endogenous virus synthesis could be induced. (19 refs.)

77-5813 Host-Dependence of the Transcription of the Genome of Herpes Simplex Virus Type 1 (Meeting Abstract). (Ita.) Costanzo, F. (Istituto di Microbiologia e Virologia, Università di Bologna, Bologna, Italy); Campanelli-Fiume, G.; Foa-Tomasi, L.; Cassai, E. *Ann Sclav* 18(6): 878-879; 1976. (3 refs.)

77-5814 Damage and Repair of DNA in Rabbit Kidney Cells Infected with Herpes Simplex Virus Type 2 (Meeting Abstract). (Eng.) Gundberg, C. M. (Boston Univ. Graduate Sch., Boston, MA 02215). *Diss Abstr Int [B]* 38(4): 1689; 1977. (no refs.)

77-5815 Transfer of the Gene for Thymidine Kinase to Thymidine Kinase-deficient Human Cells by Purified Herpes Simplex Viral DNA. (Eng.) Bacchetti, S. (Dept. Pathology, McMaster Univ., Hamilton, Ontario, Canada L8S 4J9); Graham, F. L. *Proc Natl Acad Sci USA* 74(4): 1590-1594; 1977.

The gene code for a thymidine kinase (ATP:thymidine 5'-phosphotransferase) was transferred to human thymidine kinase-negative (TK-) line 143 cells by infection with purified, sheared herpes simplex virus (HSV-2) cells. When a selective α -HAT medium [α minimal essential medium (MEM) with hypoxanthine, aminopterin, and thymidine] was used, colonies appeared within 7-10 days of incubation and several lines could be established. Thus, copies of the viral gene could be inherited by daughter cells at each division. The average specific activity of viral DNA was about 1.5 colonies/ μ g DNA for up to a max of one transformant/ 10^5 treated cells. Established lines expressed an enzymatic activity coded for by the HSV-2 genome. When colonies were challenged with α -MEM containing bromodeoxyuridine at 30 μ g/ml, cells showed differences in stability of enzyme expression that tended to be inherited by a given cell's progeny. Colonies derived from transformed cells showed variable and complex patterns of ³H-thymidine incorporation. (23 refs.)

77-5816 **Oncogenic Transformation of Rat Embryo Fibroblasts with Photoinactivated Herpes Simplex Virus: Rapid In Vitro Cloning of Transformed Cells.** (Eng.) Kucera, L. S. (Dept. Microbiology and Immunology, Bowman Gray Sch. Medicine, Wake Forest Univ., Winston-Salem, NC 27103); Gusdon, J. P.; Edwards, I.; Herbst, G. *J Gen Virol* 35(3): 473-485; 1977.

The virological, immunological, and oncogenic properties of rat embryo fibroblasts (REF) transformed by photoinactivated herpes simplex virus (HSV) were investigated. Approx 5×10^6 REF cells were suspended in 20 ml of buffered saline containing photoinactivated virus at a multiplicity of infection of 0.5. Upon in vitro cloning, only transformed REF (t-REF) line G cells grew into cell colonies that could become established clonal cell lines (63 colonies/ 1×10^4 cells). Non-transformed REF cells did not produce tumors in newborn rats over a period of > 12 ml. However, the uncloned parental line (t-REF, line G) was tumorigenic in 49% of the rats, with a latent period of 20-24 wk. The three cloned transformed lines varied from nononcogenic (clone 2) to clones (1 and 3) that produced tumors in 50% and 92% of the rats with latent periods of 10-14 wk. When t-REF-line G-clone-1 cells were passaged 30 times in vitro, the cells were extremely oncogenic in newborn rats: 100% had tumors with a latent period of 2-3 wk. Tumor cells (rat fibrosarcoma, RFS 12-22-75) established in culture produced tumors within 2 wk after subinoculation of weanling rats (100% with tumors), and they were transplantable to 100% of inoculated adult rats. Histopathologically, all tumors were large, poorly differentiated, malignant fibrosarcomas. The in vitro procedure for cloning transformants segregated clones ranging from nononcogenic to more oncogenic than the original uncloned parent cell line, and it might be useful in elucidating HSV oncogenesis. Transformation by HSV may involve defective viruses that have lost their capacity for replicating new infectious virus but retain their oncogenicity. (20 refs.)

77-5817 **Anatomy of Herpes Simplex Virus DNA. IX. Apparent Exclusion of Some Parental DNA Arrangements in the Generation of Intertypic (HSV-1 x HSV-2) Recombinants.** (Eng.) Morse, L. S. (Marjorie B. Kovler Viral Oncology Labs., Univ Chicago, Chicago, IL 60637); Buchman, T. G.; Roizman, B.; Schaffer, P. A. *J Virol* 24(1): 231-248; 1977.

The structure of herpes simplex virus (HSV) was examined in 28 recombinants between HSV-1 and HSV-2. The strains of HSV used were HSV-1 (KOS tsE6), HSV-1 (17 tsJ), HSV-1 (HFEM tsN102), HSV-2 (186 tsB5), HSV-2 (186), and HSV-2 (GP6). Two types of parental crosses were used: (1) temperature-sensitive (ts) mutants were crossed to produce wild-type recombinants; and (2) ts mutants of HSV-1 made resistant to phosphonoacetic acid were crossed with wild-type HSV-2, and recombinants that multiplied at the nonpermissive temperature and were resistant to the drug were isolated. Mapping was done by restriction endonuclease digestion.

There was a colinear arrangement of the HSV-1 and HSV-2 DNA's. The crossover of the genetic material ranged from exchange of the entire L or S component to substitutions of regions within the same component. In some recombinants, the reiterated sequences *ab* and *ac* bracketing the L and S components were heterotypic. Crossovers ranged from one to six per DNA, and clustering of crossover events was also observed. There was a definite preference for crossovers within certain regions. The phosphonoacetic acid-resistant gene was mapped between positions 0.43 to 0.52. The data are consistent with the hypothesis that only one arrangement of the parental DNA participates in the generation of recombinants. (42 refs.)

77-5818 **Mechanism of Infection by Epstein-Barr Virus. II. Comparison of Viral DNA from HR-1 and Superinfected Raji Cells by Restriction Enzymes.** (Eng.) Lee, Y. S. (Dept. Microbiology, Rush-Presbyterian-Saint Luke's Medical Center, 1753 W. Congress Parkway, Chicago, IL 60612); Yajima, Y.; Nonoyama, M. *Virology* 81(1): 17-24; 1977.

Restriction endonuclease analysis of HR-1 virus DNA and RS virus DNA was performed to compare the two kinds of Epstein-Barr virus (EBV) DNA. RS virus DNA isolated from Raji cells superinfected with EBV from P3HR-1 cells was compared with the original superinfecting virus DNA via agarose-gel electrophoresis after digestion with *Eco*R1, a restriction endonuclease derived from *Escherichia coli* RY 13. *Eco*R1 digestion of HR-1 virus DNA produced 15 fragments that were identical to those found with RS virus DNA. Two unmatched HR-1 fragments (10×10^6 and 4.6×10^6 daltons) were also found. The *Eco*R1 No. 4 (13.5×10^6 daltons) fragment of RS virus DNA showed a molar ratio of 2, but HR-1 virus DNA produced the same fragment with a molar ratio of 1. Electrophoresis following digestion with *Hind* III, *Bam* H-I, *Hpa* I, and *Sal* I endonucleases yielded similar patterns for the two types of virus, with only minor differences in molar ratios. This suggests that RS virus DNA obtained from superinfected Raji cells is basically identical to, although more heterogeneous than, HR-1 virus DNA. (17 refs.)

77-5819 **Electron Microscopy and Detection of Lymphoid Cells Bearing Epstein-Barr Virus (Meeting Abstract).** (Ita.) Falcieri, E. (Istituto di Microscopia Elettronica Clinica, Universita de Bologna, Bologna, Italy); Zerbini, M. *Ann Sclavo* 18(6): 893-894; 1976. (4 refs.)

77-5820 **Differential Induction of Epstein-Barr Virus-related Antigens in Heterokaryon Cultures.** (Eng.) Yamamoto, K. (Dept. Virology, Cancer Inst., Hok-

kaido Univ. Sch. Medicine, Sapporo 060, Japan); Osato, T. *Int J Cancer* 19(6): 767-774; 1977.

Indirect immunofluorescence studies were made of heterokaryons produced by the UV-inactivated Sendai virus-mediated fusion of ³H-thymidine labeled producer and non-producer human lymphoblastoid cells with various other cell types to investigate the induction of Epstein-Barr virus (EBV) antigenic markers. When producer P3HR-1 and QIMR-WIL cells (normally 3%-5% positive) were kept under conditions of < 0.3% expression and fused with FL and HeLa cells derived from human amnion and cervical carcinoma tissues, respectively, virus-related early antigens (EA) were first noted as early as after 3 hr. The frequency increased rapidly and reached a max (30%) after 2 days. Viral capsid antigen (VCA) appeared later, at 12 hr after fusion. In contrast, only EA could be detected in heterokaryons between nonproducer Raji or NC-37 cells and FL or HeLa cells. No significant induction was noted in heterokaryons with mouse C11D or MCB-2 cells, and EA was induced in only 10% of the heterokaryons between P3HR-1 and monkey (Vero) cells. Treatment of fused cultures with 100 µg/ml 5-iododeoxyuridine significantly enhanced EA and VCA induction. (49 refs.)

77-5821 Some Factors Affecting the Expression of Epstein-Barr Virus-Associated Membrane Antigens. (Eng) Kish, M. L. (Dept. Surgery Res., Univ. Virginia Medical Center, Box 263, Charlottesville, VA 22903); Young, B. G. *J Natl Cancer Inst* 59(5): 1375-1381; 1977.

The effects of L-arginine concentration (0.0 to 20.0 mM) and phytohemagglutinin (PHA) on the expression of Epstein-Barr virus (EBV)-associated membrane antigens (MA) were studied. At the beginning of the study, the lymphoblastoid cell line AV-1 (an EBV-producer line) demonstrated 17%-25% MA-positive cells, but 10 mo later these cells showed only 4%-12% MA-positive cells. At most of the arginine concentrations, the number of MA-positive cells decreased during the first 24 hr, increased markedly by 48 hr, and then decreased slightly between 48 and 72 hr. Statistical analysis of these results showed no significant differences among any of the arginine concentrations in their effectiveness in stimulating MA production. PHA treatment of AV-1 cells caused a rapid increase in MA-positive cells by 24 hr, followed by a rapid decline within the next 24 hr. Treatment of a nonproducer cell line (NC37) with PHA caused a marked production of MA within the first 24 hr (to approx 10% MA-positive cells) followed by a gradual decline over the next 48 hrs. Unstimulated NC37 rarely (< 1.0%) had MA. These results were discussed in relation to the cell-cycle dependence of arginine concentration for virus activation and PHA stimulation of DNA synthesis with activation of the viral genome. (22 refs.)

77-5822 Detection of Epstein-Barr Virus Antigens with Enzyme-conjugated Antibody. (Eng) Granlund,

D. J. (Dept. Virology and Cell Biology, Litton Bionetics, Incorporated, 5516 Nicholson Lane, Kensington, MD 20795); Andrese, A. P. *Int J Cancer* 20(4): 495-499; 1977.

Monospecific conjugated (fluorescein isothiocyanate and horseradish peroxidase) goat antisera, prepared against three human immunoglobulin (Ig) classes, IgM (µ), IgG (γ), and IgA (α), were compared for their ability to detect human Ig classes possessing specificity for Epstein-Barr virus (EBV) viral capsid antigens (VCA) in a chronically infected human lymphoid cell line, P3J-HRIK. The enzyme system was significantly more sensitive than immunofluorescence in detecting most of the serum in Ig cancer patients. Some patients with nasopharyngeal carcinomas (NPC) had extremely high levels of EBV-specific IgA. Patients with cancers other than NPC may have had lower EBV-specific IgA titers. (5 refs.)

77-5823 EBV-Specific IgA and Nasopharyngeal Carcinoma (Meeting Abstract). (Fre.) Desgranges, C. (Centre International de Recherche sur le Cancer, Lyon, France); Li, Y.; de The, G. B. *Ann Immunol (Paris)* 128C(4/5): 936; 1977. (no refs.)

77-5824 Antibodies to Epstein-Barr Virus Capsid Antigen and Early Antigen in Nasopharyngeal Carcinoma and Comparison Groups. (Eng) Lin, T. M. (Dept. Public Health, Natl. Taiwan Univ. Coll. Medicine, Taipei, Taiwan, Republic of China); Yang, C. S.; Chiou, J. F.; Tu, S. M.; Chen, T. Y.; Tu, Y. C.; Lin, P. J.; Kawamura, A.; Hirayama, T. *Am J Epidemiol* 106(4): 336-339; 1977.

Antibodies to Epstein-Barr virus capsid antigen (anti-VCA) and early antigen (anti-EA) were measured in 263 Taiwanese patients with nasopharyngeal carcinoma (NPC), 624 age- and sex-matched neighborhood controls, 570 family members of NPC patients, and 830 family members of the controls. The distribution of antibody titers was significantly different between NPC patients and the other three groups. More than 55% and 45% of NPC patients had titers of ≥ 1:640 and ≥ 1:80 for anti-VCA and anti-EA, respectively, but < 6.7% and < 2.5% of the other three groups had such high titers. The geometric means of anti-VCA and anti-EA titers were 1:352 and 1:45, respectively, in NPC patients compared with < 1:77 and < 1:12, respectively, in the comparison groups. Anti-VCA and anti-EA titers were significantly correlated. The association of EBV with NPC is discussed. (14 refs.)

77-5825 A Cluster of Epstein-Barr Virus-associated American Burkitt's Lymphoma. (Eng.) Judson, S. C. (699 Rural Ave., Williamsport, PA 17701); Henle, W.; Henle, G. *N Engl J Med* 297(9): 464-468; 1977.

An unusual cluster of four Epstein-Barr virus (EBV)-associated cases of Burkitt's lymphoma occurred in four

young adults (2 women aged 21 and 32 yr and two men aged 31 and 32 yr) within a 1-yr period. They lived within 50 km of each other, in rural Pennsylvania. Two patients were related by marriage, but there was no contact between the other two. All four had antibody titers to EBV-related antigens. EBV-associated nuclear-antigen-positive cells and EBV DNA were detected in the tumor samples available from three patients. These cases are unusual because time-space clustering of Burkitt's lymphoma associated with EBV has been observed thus far only in Africa. Environmental studies have failed to indicate conditions common to all four patients that would explain the cluster or provide clues of potential cofactors. (23 refs.)

7-5826 **Comparison of Epstein-Barr Viral DNAs in Burkitt Lymphoma Biopsy Cells and in Cells Clonally Transformed In Vitro.** (Eng) Sugden, B. (McArdle Lab., Univ. Wisconsin, Madison, WI 53706). *Proc Natl Acad Sci USA* 74(10): 4651-4655; 1977.

The nucleotide sequences of intracellular Epstein-Barr virus (EBV) DNAs in Burkitt's lymphoma biopsy cells and in cells clonally transformed in vitro were compared by determining the electrophoretic mobilities of restriction endonuclease cleavage fragments of the viral DNA. To carry out this comparison, cleaved cell DNAs were electrophoresed on agarose gels and transferred to nitrocellulose paper, and the immobilized viral species were identified by hybridization with purified viral DNA labeled in vitro. The complexities of all of the intracellular viral DNA were similar to one another and to that of purified virion DNA. There were small differences in the cleavage patterns of some viral DNAs, but the cleavage pattern differences for the viral DNA in the tumor cells and in the cells transformed in vitro were not more pronounced than those between the different clones of cells transformed in vitro. All the viral DNA species contained a repeated sequence. The first two findings indicate that the EBV is indistinguishable from that associated with Burkitt's lymphoma. (16 refs.)

7-5827 **Acquisition of Additional Polypeptides in Adenovirus Produced on Burkitt Lymphoma Cells (Meeting Abstract).** (Eng) Faucon, N. (Unite de Virologie, INSERM, Groupe 33, CNRS, 1 place Pr J. Renaut, 69371 Lyon Cedex 2, France); Chardonnet, Y.; Chantepie-Luray, J. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 55; 1977. (no refs.)

7-5828 **Expression of Adenovirus Antigens in Lymphoblast Lines from Burkitt's Lymphoma (Meeting**

Abstract). (Fre.) Faucon, N. (Unite de Virologie, INSERM 51, CNRS GR 33, Lyon, France); Chardonnet, Y. *Ann Immunol (Paris)* 128C(4/5): 957-958; 1977. (no refs.)

77-5829 **Genetic Analysis of Adenovirus Type 2. VII. Cleavage-modified Affinity for DNA of Internal Virion Proteins.** (Eng.) Amin, M. (Departement de Microbiologie, Centre Hospitalier Universitaire, Universite de Sherbrooke, Quebec, Canada, J1H 5N4); Mirza, A.; Weber, J. *Virology* 80(1): 83-97; 1977.

The structure and composition of the cores of a temperature-sensitive mutant (ts1) and its parental strain, wild-type (wt) adenovirus 2 (Ad2), were analyzed biochemically and by electron microscopy (EM). Since disintegration with Sarkosyl yields a core containing only viral DNA and polypeptide VII, the cores and possible intermediates of wt and ts1 were compared using this anionic detergent. Upon disintegration, 60% of ts1 at 39°C (ts1-39) was converted into subviral structures ranging from 1.50 to 1.72 g/ml in density (in CsCl), but only 35% of wt was converted into cores of density 1.58. The ts1-39 core was highly unstable and showed a tendency to move to a higher density because of lability of the DNA-protein interaction. Cores from wt and ts1-39 both contained predominantly polypeptide VII. Significantly, Pre-VII, the principal form of this polypeptide in ts1-39 virions, was completely absent from the cores. EM revealed no qualitative differences between the wt ts1-33 and ts1-39 cores in either their kinetics of unfolding or in their final DNA structure, although the ts1-39 cores unfolded more rapidly in the presence of high salt (CsCl). For comparison, the viruses were also disintegrated with pyridine. Polypeptide analysis of the pyridine cores showed significant differences between wt and ts1: wt contained polypeptides V, VII, and 14K; ts1-33 contained V, Pre-VII, VII, traces of IVa2, Pre-VI, VI, and, possibly, IX and X; ts1-39 contained V, Pre-VI, and Pre-VII. The results show significant differences in the stability and polypeptide composition of wt and ts1 cores under different conditions of disintegration. (28 refs.)

77-5830 **Further Mapping of Late Adenovirus Genes by Cell-free Translation of RNA Selected by Hybridization to Specific DNA Fragments.** (Eng) Lewis, J. B. (Cold Spring Harbor Lab., Cold Spring Harbor, NY 11724); Anderson, C. W.; Atkins, J. F. *Cell* 12(1): 37-44; 1977.

RNA isolated from the cytoplasm of human cells late after infection with adenovirus type 2 (Ad2) was fractionated by hybridization to fragments of Ad2 DNA that were produced by digestion with the restriction endonucleases Hpa I, Eco RI, Bam HI and Hind III. Cell-free translation of these partially purified mRNA's indicates that the genes for the late Ad2 proteins lie within the following intervals on the conventional Ad2 map: 15K (4.4-17.0 map units), IX and IVa₂ (7.5-17.0), IIIa (29.1-40.9), III and V (29.1-57.0), pVIII (40.9-57.0),

pVI and II (40.9-70.7), 100K (59.0-83.4), pVIII (70.7-83.4), and IV (85.0-100). In addition to the primary hybridization of the late Ad2 mRNA's to these regions, most late Ad2 mRNA's (except those for 15K, IX and IVa₂) exhibited some hybridization to a secondary site between 17.0 and 29.1 map units. (18 refs.)

- 77-5831 The Definition of a Large Viral Transcription Unit Late in Ad2 Infection of HeLa Cells: Mapping of Nascent RNA Molecules Labeled in Isolated Nuclei.** (Eng) Weber, J. (Rockefeller Univ., New York, NY 10021); Jelinek, W.; Darnell, J. E. *Cell* 10(4): 611-616; 1977.

A major transcription product was identified by labeling nuclei isolated from HeLa cells 15 hr after infection with adenovirus type 2 (Ad2). The resulting RNA transcript was approx 25 kilobases long, and it began between 0.2 and 0.3 on the physical map, extending to (or near) the right end of the genome. Most (60%-92%) of the RNA transcribed from fragments between 0.2 and 1.0 is synthesized as part of this large molecule. (34 refs.)

- 77-5832 Adenovirus Type 2 Early Nuclear and mRNA: Kinetic Estimation of *l* and *r* DNA Strand Fractions Complementary to Different Abundance Classes of Viral RNA.** (Eng) Wold, W. S. (Inst. Molecular Virology, Saint Louis Sch. Medicine, St. Louis, MO 63110); Green, M.; Brackmann, K. H.; Devine, C.; Cartas, M. A. *J Virol* 23(3): 616-625; 1977.

Vast excesses of early whole-cell RNA (WC-RNA), nuclear RNA (nRNA), and polyribosomal RNA (pRNA) extracted from KB cells infected by adenovirus 2 (Ad2) were annealed in liquid to separated Ad2 ³²P-labeled *l* (heavy) and *r* (light) DNA strands (200 to 400 nucleotides long). Hybridization kinetic data were analyzed to estimate the number of viral RNA abundance classes, their relative concentrations, and the fractions of DNA strands from which they originated. Both WC-RNA and nRNA contained at least two distinct kinetic classes and annealed to about 60% of *l* strand and 40% of *r* strand. pRNA appeared to contain three classes, abundant, scarce, and very scarce, and generally annealed to only about 14% of *l* strand. Thus, WC-RNA and nRNA contain viral DNA sequences not detectable in pRNA, indicating that portions of Ad2 DNA are transcribed into RNA molecules that are not exported to polyribosomes. Results indicate that the abundant and scarce pRNA classes may represent viral messenger RNA. For about 60% of the genome, *l*-strand-specified RNA appears to be in greater concentration than the *r*-strand type, which predominates for the remaining 40%. (24 refs.)

- 77-5833 Two Adenovirus mRNAs Have a Common 5' Terminal Leader Sequence Encoded at Least 10**

kb Upstream from Their Main Coding Regions. (Eng) Klesig, D. F. (Cold Spring Harbor Lab., Cold Spring Harbor, NY 11724). *Cell* 12(1): 9-21; 1977.

The messenger RNA's (mRNA's) encoding two late adenovirus serotype 2 (Ad2) proteins, fiber and 100K, were purified by hybridization to restriction endonuclease fragments of Ad2 DNA followed by electrophoresis on polyacrylamide gels containing 98% formamide. The 5' terminal oligonucleotides generated by RNase T1 digestion of the messengers were selected by dihydroxyborylcellulose chromatography. Both mRNA's gave an identical 5'-undecanucleotide with the general structure 7mG^{5'}ppp^{5'}AmC(m)U(C₄U₃)G. This undecanucleotide could be removed by mild RNase treatment from the mRNA after hybridization to DNA fragments containing the main coding sequence of the messenger. In contrast, a small region defined by Bal I-E (14.7-21) protected this undecanucleotide from RNase. A second region contained within Hind III-B (17-31.5) and Hpa I-F (25.5-27.9), although unable to protect the undecanucleotide, hybridized to both fiber and 100K mRNA's and protected a similar sequence of 100-150 nucleotides. These results suggest that both mRNA's contain a long common sequence that is complementary to at least two different sites on the Ad2 genome remote from the start of these two genes. The implications of these findings are discussed, and a general mechanism is presented for the biosynthesis of mRNA's from larger precursor molecules, based on intramolecular ligation. (34 refs.)

- 77-5834 Spliced Segments at the 5' Terminus of Adenovirus 2 Late mRNA.** (Eng) Berget, S. M. (Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA 02139); Moore, C.; Sharp, P. A. *Proc Natl Acad Sci USA* 74(8): 3171-3175; 1977.

A messenger RNA (mRNA) fraction coding for hexon polypeptide (hexon mRNA) was purified by gel electrophoresis from extracts of adenovirus 2 (Ad2)-infected cells 32 hr after infection. The mRNA sequences in this fraction were mapped between 51.7 and 61.3 units on the genome by visualizing RNA-DNA hybrids in the electron microscope. In hybrids of hexon mRNA and single-stranded restriction endonuclease cleavage fragments of viral DNA, branched forms were observed in which 160 nucleotides of RNA from the 5' terminus were not hydrogen-bonded to the single-stranded DNA. DNA sequences complementary to the RNA sequences in each 5' tail were located at 17, 20, and 27 units on the same strand as the coding for the body of the hexon mRNA. This indicates that four segments of viral RNA may be joined together during the synthesis of mature hexon mRNA. A plausible model for the synthesis of mature hexon mRNA would be intramolecular joining of the three short segments forming the 5' tail to the body of the hexon mRNA during processing of a nuclear precursor to generate mature mRNA. This would result in the maturation of one mRNA

species from each longer precursor, and it would explain the large abundance of accumulated viral RNA sequences in the nucleus of cells during the late stage of the lytic cycle. (31 refs.)

77-5835 The Physical Locations of Structural Genes in Adenovirus DNA. (Eng.) Grodzicker, T. (Cold Spring Harbor Lab., Post Office Box 100, Cold Spring Harbor, NY 11724); Anderson, C.; Sambrook, J.; Mathews, M. B. *Virology* 80(1): 111-126; 1977.

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis was used to distinguish between a number of polypeptides coded for by adenovirus type 5 (Ad5) and their counterparts coded for by Ad2+ND1, a nondefective Ad2-simian virus 40 hybrid virus. Analysis of proteins synthesized at late times after infection of HeLa cells with Ad2+ND1 and Ad5 demonstrated 20 bands not seen in extracts of uninfected cells. There were several differences in the electrophoretic behavior of Ad2+ND1- and Ad5-specific proteins: the major capsid proteins (hexon and fiber) obtained from Ad5-infected cells migrated faster than those extracted from Ad2+ND1-infected cells. Ad5 100,000-molecular wt protein migrated more slowly than the homologous polypeptide of Ad2+ND1. A protein (ND1 protein) could be detected in Ad2+ND1-infected cells but not in Ad5-infected cells. By correlating the expression of each of these polypeptides with the genetic composition of interserotypic recombinants formed between Ad5 and Ad2+ND1, the structural genes for these polypeptides were located on the Ad genetic and physical maps. This allowed the location of the structural genes to be related to the physical map position of temperature-sensitive (*ts*) mutants and assignment of the *ts* mutants to specific genes. In addition, the early Ad5 mutant *ts* 125 (which has a defect in the Ad-specific single-stranded DNA-binding protein) and an Ad2+ND1 *ts* mutant were physically mapped in the same complementation group, as a result of which the structural gene for the DNA-binding protein was located. Electrophoretic differences between the virus-associated RNA's of Ad2 and Ad5 were used to analyze the recombinants and to identify the origin of the region of DNA around position 0.3 on the viral genome. (38 refs.)

77-5836 Replication of Linear Adenovirus DNA Is Not Hairpin-primed. (Eng.) Stillman, B. W. (Dept. Microbiology, John Curtin Sch. Medicine Res., Australian Natl. Univ., Canberra, ACT 2601, Australia); Bellett, A. J. *Nature* 269(5630): 723-725; 1977.

The hairpin-priming model of adenovirus replication assumes that with each round of replication, the DNA terminal sequences must be inverted, resulting in four types of molecule differing in the order of the terminal sequences. The model also predicts a strand switch in which the original 3' terminus becomes the 5' end of the progeny strand, to be replaced by

newly replicated DNA at the 3' end of the parental strand. Evidence against these hypotheses is presented. An alternative model for adenovirus DNA replication is proposed in which the terminal 55,000-mol wt protein binds deoxycytidine and recognizes the free 3'-OH to prime DNA synthesis. The model suggests a function for both the 55,000-mol wt protein and terminal repetition. (22 refs.)

77-5837 Loop Structures in Hybrids of Early RNA and the Separated Strands of Adenovirus DNA. (Eng.) Kitchingman, G. R. (Section Animal Viruses, Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD 20014); Lai, S. P.; Westphal, H. *Proc Natl Acad Sci USA* 74(10): 4392-4395; 1977.

Separated strands of adenovirus type 2 DNA were annealed with early cytoplasmic RNA and visualized in the electron microscope. DNA-RNA duplex regions within the DNA filaments could be recognized by their heavy contour. This contour was often interrupted at distinct locations by loops of displaced, single-stranded DNA. Loops have been observed and mapped in all four early regions of the genome. The structures appear to signal hitherto unknown mechanisms of eukaryotic gene expression. (33 refs.)

77-5838 Evidence from UV Transcription Mapping in HeLa Cells That Heterogeneous Nuclear RNA Is the Messenger RNA Precursor. (Eng.) Goldberg, S. (Rockefeller Univ., New York, NY 10021); Schwartz, H.; Darnell, J. E. *Proc Natl Acad Sci USA* 74(10): 4520-4523; 1977.

The effects of UV irradiation on the incorporation of ³H-uridine in HeLa cell messenger RNA (mRNA), ribosomal RNA, heterogeneous nuclear RNA (hnRNA), and early mRNA from adenovirus type 2 was compared. The UV target size of cell mRNA was at least three times larger than the average size of the mRNA itself and larger than the adenovirus-2 early mRNA, which is known to derive from transcription units of about 1.5-5.0 kilobases. The UV target size of hnRNA, in contrast, was about the same as its size, determined by sedimentation, and it overlapped with the target size of mRNA. It is concluded that most mRNA derives from a higher mol wt hnRNA molecule. (21 refs.)

77-5839 Replication of Adenovirus Type 2 DNA In Vitro. (Eng.) Kaplan, L. M. (Dept. Cell Biology, Albert Einstein Coll. Medicine, 1300 Morris Park Ave., Bronx, NY 10461); Kleinman, R. E.; Horwitz, M. S. *Proc Natl Acad Sci USA* 74(10): 4425-4429; 1977.

A soluble replication system was developed that synthesized full-size adenovirus DNA molecules. The extraction of in-

infected HeLa nuclei solubilized approx 25% of the viral replicating DNA and left the HeLa chromatin associated with the insoluble nuclear material. Both the extracted viral DNA and the DNA product synthesized in vitro were intact and identical to the adenovirus DNA or its replicating intermediates produced in whole infected cells. The direction of elongation and the replication termini of progeny DNA in vitro were essentially identical to those observed in vivo. Nuclear extract replication was dependent on Mg^{2+} and the four deoxyribonucleoside triphosphates, and it was partially stimulated by ATP. (38 refs.)

- 77-5840 **Enzymatic Properties of Viral Replication Complexes Isolated from Adenovirus Type 2-infected HeLa Cell Nuclei.** (Eng) Brison, O. (Laboratoire de Biologie Moléculaire des Cellules Eukaryotes du Centre National de la Recherche Scientifique, U44 de l'Institut National de la Santé et de la Recherche Médicale, Faculté de Médecine, 67085 Strasbourg Cedex, France); Kedinger, C.; Wilhelm, J. *J Virol* 24(2): 423-435; 1977.

The enzymatic properties of viral replication complexes from HeLa cells infected with adenovirus type 2 (Ad2) were determined 17 hr after infection. Extraction of the complexes with 200 mM ammonium sulfate revealed that the DNA polymerase isolated depended on the presence of a divalent cation and the four deoxyribonucleoside triphosphates. Two types of DNA polymerase were present: free enzyme molecules that could readily initiate on an activated template at low ionic strength and enzyme molecules consisting of elongating DNA chains that were not blocked by 200 mM ammonium sulfate. The elongating chains that could not be blocked by high salt concentrations corresponded to strands that had been initiated in vivo and were elongating in vitro. The total DNA polymerase activity represented 35% of that at high salt concentrations. The Ad2 DNA synthesis in this fraction replicated semiconservatively, and at least part of the molecules belonged to the γ class. The possibility that γ activity was also present but was lost during purification could not be excluded. (40 refs.)

- 77-5841 **Physical Organization of Subgroup B Human Adenovirus Genomes.** (Eng) Tibbetts, C. (Dept. Microbiology, Sch. Medicine, Univ. Connecticut Health Center, Farmington, CT 06032). *J Virol* 24(2): 564-579; 1977.

The genome of viral DNA from adenovirus type 3 (Ad3) and Ad7, serotypes representing subgroup B human adenoviruses, was mapped using *EcoRI*, *Sal I*, *Xba I*, *Hpa I*, *Kpn I*, *Xho I*, *Sma I*, *Bam I*, and *HindIII*. Of 94 sites mapped, 82 were common to both serotypes; this agreed with the overall

sequence homology of DNA among members of the same subgroups. The fraction of the genome length occupied by fragments from each enzyme is illustrated. However, < 20% of the mapped sites corresponded to sites in Ad2 or Ad5 serotypes of subgroup C. Hybridization mapping of viral messenger RNA from Ad7-infected cells resulted in a physical map that was nearly identical to that of early and late gene clusters in Ad2 DNA. Thus, although the organization of subgroups B and C adenovirus genomes may be virtually identical, the DNA sequences have diverged significantly in viral evolution. (28 refs.)

- 77-5842 **Human Polyoma Viruses (JC-BK) in Renal Transplant Patients (Meeting Abstract).** (Eng.) Hogan, T. F. (Dept. Medical Microbiology, Univ. Wisconsin, Madison, WI 53706); Borden, E. C.; Padgett, B. L.; Walker, D. L.; Hussey, J. *Clin Res* 25(4): 586A; 1977. (no refs.)

- 77-5843 **High Incidence of Ependymomas Induced by BK Virus, a Human Papovavirus: Brief Communication.** (Eng) Corallini, A. (Inst. Microbiology, Univ. Ferrara, Via Luigi Borsari 46, 44100 Ferrara, Italy); Barban-ti-Brodano, G.; Bortoloni, W.; Nenci, I.; Cassai, E.; Tampieri, M.; Portolani, M.; Borgatti, M. *J Natl Cancer Inst* 59(5): 1561-1564; 1977.

The oncogenicity of crude and purified BK virus (BKV) was tested in Syrian golden hamsters and outbred Swiss mice. Newborn hamsters inoculated sc or ip with a crude virus inoculum of 5.7 (\log_{10} of fluorescent antibody focus-forming units) did not develop any tumors; the same result was observed with an inoculum of 4.7 injected intracerebrally (ic). Iv treatment with an inoculum of 6.4 to 3- to 4-wk-old hamsters produced tumors in 2/89. Sc and ip injection of a purified virus inoculum of 7.7 resulted in a tumor incidence of 1/43 and 0/34 hamsters, respectively, and 0/39 and 0/27 mice. However, treatment ic with an inoculum of 7.3 resulted in tumors in 44/50 hamsters and 9/31 mice. All tumors except one fibrosarcoma were ependymomas. T antigen was found in 3/3 hamsters tested by immunofluorescence (IF) and in 12/14 hamsters and 3/3 mice tested by complement fixation (CF). Antibodies to T antigen were examined in hamsters only, and they were found in 5/14 by IF, 6/14 by CF, and 13/14 by hemagglutinin inhibition. BKV could be rescued from the fibrosarcoma and the ependymomas by Sendai virus-mediated fusion with Vero cells. These studies demonstrate the oncogenicity of BKV in rodents. (21 refs.)

- 77-5844 **Condylomata Acuminata Associated with Morbus Bowen (Carcinoma In Situ): A Light and**

Electron Microscopic Study. (Eng.) Grussendorf, E. I. (Dept. Dermatology, Medical Faculty, RWTH Aachen, Goethestrasse 27-29, D-51 Aachen, W. Germany); Bar, T. *Dermatologica* 155(1): 50-58; 1977.

Light and electron microscopy studies were made of a case of condylomata acuminata (genital warts) associated with Morbus Bowen. They revealed a vacuolar degeneration of the cytoplasm that was believed to be characteristic of papova virus infection and nuclear alterations, such as the formation of nuclear inclusions, which might be virus particles. The evidence is suggestive of papova virus infection. (26 refs.)

77-5845 Identification of an Immunologically Distinct Papillomavirus from Lesions of Epidermodysplasia Verruciformis. (Eng) Pass, F. (Dept. Dermatology, Univ. Minnesota Medical Sch., Minneapolis, MN 55455); Reissig, M.; Shah, K. V.; Eisinger, M.; Orth, G. *J Natl Cancer Inst* 59(4): 1107-1112; 1977.

Virions isolated from warts of two siblings with epidermodysplasia verruciformis (EV), a rare disease characterized by the lifelong growth of warty skin tumors containing papovavirions, were compared with isolates of human papillomavirus (HPV) from three pools of plantar and common hand warts. The length of relaxed, circular (form II) molecules of EV virion DNA approximated the length of HPV DNA but it was 3.3% longer. Rabbit antisera against the three HPV pools coated and aggregated HPV in immune electron microscopy (IEM) tests but did not react with EV virions. These antisera reacted at high titers in complement fixation (CF) tests with HPV and reacted only weakly in CF tests with EV virions. Although rabbit antisera to EV virions coated and aggregated EV virions, they reacted only weakly or not at all with HPV virions in IEM tests. These sera reacted in CF with EV virions only. The data indicate that virions from the EV patients represent an immunologically distinct papillomavirus. (25 refs.)

77-5846 Characterization of a New Type of Human Papillomavirus That Causes Skin Warts. (Eng) Orth, G. (Unite de Recherches sur l'Etiologie Virale des Cancers Humains, Laboratoire 147 associe au Centre National de la Recherche Scientifique, Institut Gustave-Roussay, 94800 Villejuif, France); Favre, M.; Croissant, O. *J Virol* 24(1): 108-120; 1977.

A human papillomavirus (HPV) was isolated from the lesions of a patient (ML) with numerous common warts on both hands. This virus was compared with the HPV found in typi-

cal plantar warts (plantar HPV). ML and plantar HPV DNA's had similar mol wts (5.26×10^6 and 5.23×10^6 , respectively) but were shown to differ by restriction enzyme analysis. The cleavage products of ML HPV DNA differed from those of plantar HPV DNA in both fragment number and size. In contrast to plantar HPV DNA, a high proportion of ML HPV DNA molecules were resistant to the restriction enzymes. Most, if not all, of the molecules were resistant to *Bam*I and sensitive to *Eco*RI or vice versa. After denaturation and renaturation of the cleavage products of ML HPV DNA by a mixture of the two enzymes, the circular heteroduplexes formed showed one to three heterology loops corresponding to 4%-8% of the genome length. No sequence homology was detected between ML and plantar HPV DNA's by complementary RNA (cRNA)-DNA filter hybridization, by measuring the reassociation kinetics of iodinated plantar HPV DNA in the presence of a 25-fold excess of ML HPV DNA, or by the heteroduplex technique. The two viruses had distinct electrophoretic polypeptide patterns and showed no antigenic cross-reaction in immunodiffusion or immunofluorescence tests. Preliminary cRNA-DNA hybridization experiments, using viral DNA's from single or pooled plantar or hand warts, suggest that common hand warts are associated with viruses or similar or related to ML HPV. The existence of at least two distinct types of HPV's that cause skin warts was demonstrated; they were provisionally called HPV type 1 and HPV type 2, with plantar HPV and ML HPV as the prototypical viruses, respectively. (37 refs.)

77-5847 Comparative Study of Delayed Hypersensitivity Skin Reactions and Antibodies to Human Papilloma Virus (HPV). (Eng) Viac, J. (Clinique Dermatologique, Hopital E. Herriot, Lyon, France); Thivolet, J.; Hegazy, M. R.; Chardonnet, Y.; Dambuyant, C. *Clin Exp Immunol* 29(2): 240-246; 1977.

Purified human papilloma virus (HPV) was prepared from plantar warts, inactivated by formalin, adjusted to 10^{10} particles/0.1 ml, and used in id tests (IDT) on 120 patients with warts at the time of testing or in the past, plus 63 controls. Antibodies in patients sera were evaluated by indirect immunofluorescence (IF) test before and after the skin tests. The results showed a specific delayed-hypersensitivity reaction (DHR) to HPV, especially in patients with regressing or past warts (76%). The DHR was most frequent in patients with a wart of 6 mo-2 yr duration (77.0%-68.8%), and it persisted much longer than antibodies, which disappeared with the passage of time. The incidence of antibodies was much higher after IDT in patients with a positive reaction, suggesting a booster effect. The results indicate that cell-mediated immune responses play a major part in wart regression. (27 refs.)

77-5848 **Evidence for the Presence of Oncorna Viruses in Spleen Tissue from Patients with Haematological Malignancies (Meeting Abstract).** (Eng) van Muijen, G. N. (Lab. for Pathology, State Univ. Leiden, The Netherlands); Warnaar, S. O. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977.* International Agency for Research on Cancer. (Lyon, France): p. 51; 1977. (no refs.)

77-5849 **Isolation of a Leukemogenic Virus from Human Leukemic Bone Marrow by Cocultivation Procedures (Meeting Abstract).** (Eng) Nooter, K. (Radiobiological Inst. TNO, Rijswijk, The Netherlands); Bentvelzen, P.; Coolen, J. C.; Zurcher, C. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977.* International Agency for Research on Cancer. (Lyon, France): p. 51; 1977. (no refs.)

77-5850 **Possible Viral Involvement in Human Mammary Carcinoma: A Microwave and Laser-Raman Study.** (Eng) Webb, S. J. (Physics Dept., Univ. South Florida, Tampa, FL 33620); Lee, R.; Stoneham, M. E. *Int J Quantum Chem Quantum Biol Symp* (4): 277-284; 1977.

Normal human mammary tissues and mammary carcinoma tissues were studied by microwave and laser Raman spectroscopy. The spectra indicate that resonances between 10^{10} and 10^{12} hertz exist in active cells. The spectra of both normal and tumor cells from breast cancer patients displayed a splitting of the single peaks seen in the spectra of normal cells from cancer-free patients. The same peak-splitting occurred when baby hamster kidney cells in tissue culture were transformed into tumor cells by murine sarcoma viruses. The results suggest that in vivo coherent oscillations become resolved during oncogenesis. In addition, women who develop breast cancer may carry a latent oncogenic virus that is inducible by pregnancy, menopause, and trauma. Thus, breast cancer and even predisposition to the disease may be diagnosed spectroscopically. (18 refs.)

77-5851 **Human Mammary Gland Associated Antigens. Lack of D-Type Retravirus-induced Antigens.** (Eng) Kryukova, I. N. (Gamaleya Inst. Epidemiology and Microbiology, Acad. Medical Sciences USSR, Moscow, USSR); Bobrova, T. S. *Neoplasma* 24(2): 365-373; 1977.

Antisera (AS) against tumor-associated and organ-specific

antigens of human mammary glands and mammary carcinoma (MC) patient sera were cross-reacted in a test system for a nucleoid antigen of Hep-2 retractor virus. The antisera revealed three organ-specific antigens in the milk of a lactating MC patient, slow, medium, and fast, according to their rate of diffusion into gels. Absorption of AS against Hep-2v antigen with lyophilized milk containing the slow milk antigen did not decrease its reactivity with Hep-2 virus preparations and vice versa. Sera from slow and medium milk antigens were not cross-reactive with antigens of Hep-2v or the two MC cellular homogenates SH3 or E16b; thus, organ-specific antigens appear to be different from Hep-2v antigens. None of the density gradient zones of fractionated Hep-2 or HeLa cells were reactive with sera against MC or with slow or medium milk antigens. Since two of these fractions contained A particles, it is suggested that A-type particles in human milk are immunologically different from D-type viruses. None of the patient sera tested precipitated antigens of Hep-2v or the E16b and SH3 cellular homogenates. AS reactions suggested that the nucleoid antigen is expressed on Hep-2 cell surfaces but not on E16b cells and those of different human tumors. Precipitation experiments against E16b, SH3, and FL (human embryonic epithelium) cells suggested that the surface antigens of these lines are identical. However, a band in Hep-2 but not in E16b seemed to be formed by a viral antigen that was different from the main nucleoid antigen. Testing of the serum against gastric mucosa extracts from patients with gastric adenocarcinoma resulted in precipitin bands identical with those formed by E16b and Hep-2 cell-surface extracts. This suggests that some common stem cell, rather than a D-type virus genome, might be involved in the synthesis of the cell-surface antigen. Absorption of patient sera with human embryonic tissue did not decrease the fixed immunofluorescence. (17 refs.)

77-5852 **Virus-like Particles in a Case of Human Prostate Carcinoma.** (Eng) Ohtsuki, Y. (Dept. Virology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Seman, G.; Dmochowski, L.; Bowen, J. M.; Johnson, D. E. *J Natl Cancer Inst* 58(5): 1493-1496; 1977.

A biopsy specimen of human prostate cancer was examined by electron microscopy, and two morphologically different types of intracisternal viruslike particles were observed. Particles of one type were 150-200 nanometers (nm) in diameter and contained either an electron-dense core or two concentric inner layers. Particles of the other type were smaller, 80-100 nm in diameter, and appeared mostly in filamentous or chain-like formation. Both types of particles and budding were observed in the endoplasmic cavities of epithelial tumor cells. Morphologically, no transitional forms between the two types of particles could be described, and it seems safe to contend that they represent two distinct entities. The particles had ultrastructural characteristics that suggest a viral nature, but

ey were different from the known B-, C- or H- type (ham-
er type R) virus particles. This is the first electron micro-
opic observation in prostate cancer of viruslike particles
nilar to those previously reported in a human breast car-
oma. The significance of the association of these particles
th prostate and breast cancer is not known. (19 refs.)

-5853 **VSV Pseudotypes Produced in Human Melano-
ma Cell Lines (Meeting Abstract).** (Eng) Van
eghem, N. (Universite Libre de Bruxelles, Brussels, Belgi-
n); Liteanu, D.; Vercammen-Grandjean, A. F.; Vanden-
ssche, P.; Dekegel, D.; Beaumont, L.; Lejeune, F. J. *In:*
urth Meeting of the European Association for Cancer Re-

*search, 13th-15th September, 1977. International Agency for
Research on Cancer. (Lyon, France): p. 52; 1977. (no refs.)*

See also:

*(Rev.): 77-5422, 77-5423, 77-5424, 77-5425, 77-5426,
77-5428, 77-5429, 77-5431, 77-5432, 77-5435.

*(Chem.): 77-5497, 77-5573, 77-5583, 77-5608,
77-5622, 77-5634.

*(Immun.): 77-5860, 77-5865, 77-5866, 77-5870,
77-5871, 77-5874, 77-5877, 77-5878,
77-5880, 77-5883, 77-5884, 77-5885,
77-5888, 77-5892.

*(Path.): 77-5896.

*(Epid.-Biom.): 77-5934, 77-5958.

- 77-5854 **Some Data Concerning Immune Processes in Concomitant Tumor Immunity Experimental Models. Comparative In Vivo and In Vitro Investigations. II. In Vitro Experiments.** (Eng.) Donovan, G. (Oncological Inst., Bucharest, Romania); Popp, I.; Badea, E.; Bologa, L. *Neoplasma* 24(3): 303-310; 1977.

The humoral and cellular immune status of C57BL/6 male mice and R male rats bearing methylcholanthrene-induced sarcomas was investigated and correlated with the concomitant tumor immunity (CTI) observed in animals bearing primary tumors of different sizes. Sera from animals bearing 2%-3% tumor wt to total body wt (TW/TBW) and an efficient CTI showed antibody activity, the presence of antigen-antibody complexes, and little or no free antigen. Humoral immunity increased substantially after challenge with tumor cells. Cell mediated immunity remained low before and after challenge. In contrast, animals with a 30%-37% TW/TBW showed a disappearance of CTI coincident with a high level of free antigen and antigen-antibody complexes in the sera, but antibodies could no longer be detected. These results, along with those reported by others, are discussed, and the possible mechanisms by which serum immune factors may impair the immune status of a tumor bearer are considered. It appears that the tumor is able to annihilate the host's immune response against it, perhaps by the shedding of tumor-specific antigens and the formation of antigen-antibody complexes. (31 refs.)

- 77-5855 **Some Data Concerning Immune Processes in Concomitant Tumor Immunity Experimental Models. Comparative In Vivo and In Vitro Investigations. I. In Vivo Experiments.** (Eng.) Badea, E. (Oncological Inst., Bucharest, Romania); Donovan, G.; Dumitrescu, R.; Fadei, L.; Popp, I. *Neoplasma* 24(3): 295-301; 1977.

Concomitant tumor immunity (CTI) was studied in syngeneic male C57BL/6 mice bearing transplants of a 20-methylcholanthrene-induced sarcoma using graded challenge doses for different primary tumor sizes [2%-12% tumor wt to total body wt (TW/TBW)]. CTI decreased with increased TW/TBW. Different sc areas of the mice were equipotent for the challenge doses, and extirpation of the regional lymph node draining the primary tumor did not alter the CTI response. When the appropriate challenge dose was administered by dividing it into four inoculation sites, four tumors usually resulted. These results suggest that CTI is an expression of general immunity. Although the host exhibits antitumor immunity during a relatively long period of tumor development, a gradual curtailment of CTI capacity is correlated with increasing TW/TBW. (16 refs.)

- 77-5856 **In Vivo Immune Responses of Mice During Carcinogenesis by Ultraviolet Irradiation.** (Eng.) Kripke, M. L. (Basic Res. Program, NCI Frederick Cancer Res. Center, P.O. Box B, Frederick, MD 21701); Lofgren, J. S.; Beard, J.; Jessup, J. M.; Fisher, M. S. *J Natl Cancer Inst* 59(4): 1227-1230; 1977.

C3H/HeN(MTV-) (C3H-) mice were irradiated with UV light (wavelength range 280-340 nanometers) at an av dose rate of 2.8 Joule/m²/sec for 1 hr, 3x/w, from 22 to 42 wk. After 3 mo. usually all mice were susceptible to challenge with the three UV-induced syngeneic fibrosarcomas tested. In one of these tumors, this effect lasted up to 6 mo after cessation of UV treatments. The irradiated mice rejected tumor allografts from H-2 incompatible strains (B16 melanoma and a spontaneous leukemia) and H-2 compatible, semisyngeneic skin grafts. The primary hemagglutinin response to sheep RBC was the same in irradiated and control mice. Lymph node cells (2×10^6 or 5×10^6) from UV-irradiated mice were as competent as controls in inducing a local graft versus host response in B6C3F₁ hybrid mice. However, irradiation of the B6C3F₁ recipients for 2 or 3 mo resulted in some reductions in reactivity at the lower cell dose. The UV-irradiated C3H-mice demonstrated a normal inflammatory response to intradermal footpad injections of dimethylsulfoxide, but delayed hypersensitivity to dinitrochlorobenzene was absent in mice irradiated for 1 and 2 mo. After 3 mo of UV treatment, however, the hypersensitivity reaction was indistinguishable from unirradiated controls. It was concluded that chronic UV-irradiation does not exert a generalized immunosuppressive effect and that failure to reject autochthonous and syngeneic tumor cells may be due to neoantigens expressed on UV-transformed cells. (13 refs.)

- 77-5857 **Influence of Histones on the Development of Experimental Leukemia.** (Ukr.) Chorna, Zh. O. (Inst. Oncological Problems, Acad. Sciences Ukrainian SSR, Kiev, USSR). *Dopov Akad Nauk Ukr RSR* (7): 658-661; 1977.

The effect of histones isolated from the thymus, spleen, and bone marrow of healthy rats and from the RBC of 5-day-old chicken embryos on the development and transplantability of Svec leukemia, Pliss lymphosarcoma, NK/ly and La leukemia, and Rauscher virus leukemia was studied in C57BL and BALB/c mice and in random bred rats. The tumor cells were preincubated with histone before their sc transplantation into healthy animals. The RBC-specific histone fraction H₁, fraction H₂, which has a high lysine content, and the total embryonal histone suppressed the growth of Svec leukemia, Pliss lymphosarcoma, NK/ly and La leukemia, and Rausch-

er virus leukemia. The total histone obtained from the hematopoietic organs of healthy rats stimulated the leukemic process under the same conditions. The mechanism of the antitumor effect of exogenous histones has not yet been elucidated. (15 refs.)

77-5858 Direct and Serial Transplantation of a Ph¹ +ve Human Myeloblastoid Tumour into Nude Mice.

(Eng) Ueyama, Y. (Central Inst. Experimental Animals, Kawasaki, Japan); Morita, K.; Kondo, Y.; Sato, N.; Asano, S.; Ohsawa, N.; Sakurai, M.; Nagumo, F.; Iijima, K.; Tamaki, N. *Br J Cancer* 36(4): 523-527; 1977.

A Philadelphia chromosome (Ph¹)-positive tumor from a 67-yr-old man with chronic myelogenous leukemia was transplanted successfully into BALB/c-nu/nu mice. The 5-mm tumor blocks were implanted sc; they began to grow rapidly after about 20 days. The mice died about 8 wk after transplantation. The tumors did not adhere to the adjacent tissues, and they had been vascularized by the host. No dissemination was observed. The histology of the transplanted tumor was similar to that of the original. Karyotype studies indicated that the Ph¹ chromosome was maintained. Previous attempts at similar transplants are reviewed. (9 refs.)

77-5859 Heterotransplantation of Cultured Cells and Biopsies Derived from Nasopharyngeal Carcinoma into Thymus-less (Nude) Mice. II. Lymphoid Tissue Reaction to Metastatic Nasopharyngeal Carcinoma in Nude Mice. (Eng) Kawamura, A. (Dept. Immunology, Inst. Medical Science, Univ. Tokyo, Shirokanedai, Minato-ku, Tokyo 108, Japan); Chen, H. C.; Murata, M.; Hamajima, K.; Osono, M.; Suzuki, K.; Sudo, K.; Saito, Y.; Sairenji, T.; Hinuma, Y. *Jpn J Exp Med* 47(4): 271-294; 1977.

Human nasopharyngeal carcinomas (NPC) transplanted into nude mice retained their original architecture, except for the absence of mononuclear cell infiltration in the stromal tissue. In contrast, the inoculation of mice with cells of two established NPC lines resulted in carcinoma simplex, the most primitive type of NPC. Cultured cells derived from these tumors after their passage in mice possessed Epstein-Barr virus nuclear, membrane, capsid, and early antigens. After several passages, the heterotransplanted NPC produced a gradual decrease in the number of circulating macrophages in the medullary sinuses and lymphocyte hyperplasia. After release of the lymphocytes and macrophages into the peripheral lymph nodes, the spleen underwent extensive distortion marked by collapse of the splenic cords followed by septum formation with granulomas. In this state of immunosuppression, the NPC metastasized to the regional nodes. (104 refs.)

77-5860 Immunosuppression by Spleen Cells from Moloney Leukemia. III. Evidence for a Suppressor Cell That Is Not the Leukemic, Virus-producing Cell. (Eng) Cerny, J. (Dept. Microbiology, Harvard Univ. Sch. Public Health, Boston, MA 02115); Grinwich, K. D.; Stiller, R. A. *J Immunol* 119(3): 1097-1101; 1977.

Immunosuppressive cells from the spleens of mice bearing Moloney murine leukemia virus (MuLV)-induced leukemia were examined with anti-MuLV serum to determine whether these cells were virus-infected tumor cells or normal cells. When leukemic spleen cell suspensions were treated with syngeneic mouse anti-MuLV serum (plus complement) and with rat anti-MuLV serum (plus complement), approx 20% to 30% and 60% to 70% of the cells were killed, respectively. After anti-MuLV serum treatment, the number of MuLV-releasing cells decreased 10-fold and the leukemogenic potential in vivo decreased 100-fold. In contrast, the ability of the antisera-treated cells to inhibit the anti-sheep RBC response remained undiminished. These results indicate that the immunosuppressive cells in the leukemic spleen are normal, noninfected cells that may be involved in immune regulation. (21 refs.)

77-5861 Characterization of a Dialyzable Immunosuppressive Fraction from Mastocytoma Culture Supernatants. (Eng) Kamo, I. (Dept. Microbiology and Immunology, Albert Einstein Medical Center, Philadelphia, PA 19141); Friedman, H. *Proc Soc Exp Biol Med* 156(1): 177-180; 1977.

Dialysates from mastocytoma cell culture (PB815X) supernatants were concentrated, subjected to gel filtration using Sephadex columns, and tested for effects on antibody formation using an in vitro culture system. Supernatants incubated in serum-free medium with normal splenocytes from DBA/2 mice for 24 hr suppressed hemolysis of sheep RBC by the immunized cells. Addition of 0.5 ml supernatant to 1.5 ml culture medium resulted in $\geq 50\%$ reduction in the number of plaque-forming cells in cultures of 5×10^6 normal, immunized splenocytes. The suppressive activity was found mainly in the dialyzable portion of the supernatants, while the residual material had negligible suppressive effects. The suppressive factor appeared to have a mol wt in the 1,000 to 5,000 dalton range and was stable to heating at 56 C for 30 min but inactivated at 80 C. These results suggest that a relatively low mol wt, dialyzable material, possibly a polypeptide, is responsible for the immunosuppressive property of mastocytoma cells. (20 refs.)

77-5862 Enhanced Tumor Growth Caused by Anti-Th-B Antiserum due to a Possible Activation of Sup-

pressor T-Cells. (Eng.) Kakimoto, K. (Dept. Biochemistry, Kyushu Univ. Sch. Dentistry, Katakasu Fukuoka, Japan); Fuji, H.; Grossberg, A. L.; Pressman, D. *Cancer Res* 37(9): 3145-3150; 1977.

Injection of goat anti-Th-B antibody reagent (antiserum raised against BALB/c myeloma MOPC 104E cells and purified) into AKR mice resulted in significant enhanced growth of the allogeneic sarcoma 180. Sarcoma 180 bound essentially no anti-Th-B antibody, indicating that there was probably no direct stimulation of the tumor cells. Anti-Th-B antibodies did not decrease cytotoxic effector lymphocytes, which shows that tumor enhancement was probably not due to reduction of cytotoxic effector T cells or reduction of precursors of effector T cells. Enhancing activity for tumor growth could be transferred into mice by passive transfer of spleen cells and thymus cells collected from tumor-bearing animals previously inoculated with anti-Th-B antibodies. The tumor-enhancing effect of anti-Th-B antibodies is suggested to be mediated through the stimulation of suppressor T cells or suppressor macrophages. If a precursor of suppressor cells carries the Th-B determinant and if anti-Th-B antibody stimulates these precursor cells to mature and proliferate into a population of suppressor cells, the latter could suppress the immune mechanism(s) that causes rejection of sarcoma 180 in AKR mice. (22 refs.)

77-5863 Relationship Between Tumour Growth Rate and Proteic Variations in Interstitial Subcutaneous Fluid and Serum: Possible Thymic Control. (Eng.) Vaillier, D. (Unit Experimental Cancerology, INSERM-U.95, Plateau de Brabois, 54500, Vandoeuvre, France); Vaillier, J.; Bischoff, P. *Eur J Cancer* 13(9): 1025-1032; 1977.

The relationship between tumor growth rate and variations in protein contents of the interstitial sc fluid and serum of mice was investigated in two stimulating (S) tumors (capable of stimulating the proliferation of target cells) and two non-stimulating (NS) tumors. The methylcholanthrene-induced S tumors MC3 and RV3 exhibited a much faster growth than the NS tumors MC2 and VMM2 in normal blasts. There was a significant decrease of protein in the interstitial fluid and serum of mice bearing S tumors and a significant increase of protein in the interstitial fluid of mice bearing NS tumors. When mice carrying an MC3 tumor were implanted with an MC2 tumor, the growth of the MC2 tumor was significantly accelerated. On the contrary, when mice carrying an MC2 tumor were implanted with an MC3 tumor, the MC3 tumor growth was retarded. When MC3 and RV2 tumors were grown in T-cell-deprived mice, tumor growth was delayed significantly compared with that in normal mice; also, there was no significant decrease of serum or interstitial fluid protein. VMM2 showed a significant acceleration of growth in T-cell-deprived mice. Although there was no significant difference in growth of the MC2 tumor in normal and T-cell-deprived mice, the interstitial fluid protein was not increased.

These findings show that there is a relationship between variations in interstitial fluid and serum protein and tumor growth that might be under thymic control. (23 refs.)

77-5864 Enhanced Growth of Syngeneic Moloney Sarcoma with Decreased Immunity in the Regressors. (Eng.) Mayer, A. M. (Seccion Leucemia Experimental, Instituto de Investigaciones Hematologicas, Academia Nacional de Medicina, Las Heras 3092, 1425 Buenos Aires, Argentina); Basombrio, M. A.; Pasqualini, C. D. *Br J Cancer* 36(2): 173-176; 1977.

When fragments of Moloney sarcoma (MS) tumors were inserted into glass cylinders that had been implanted in BALB/c mice sc 2 days earlier, 51% of the animals died with progressively growing tumors (av time to death 45 days). In contrast, only 2% of mice receiving the tumor inoculum directly, sc, died. These results demonstrate that growth of a syngeneic tumor can be enhanced when the tumor is injected in an artificially constructed privileged site. Also, animals that reject these enhanced MS tumors show less cross-immunity against a lethal dose of Prececutti-Law leukemia virus (a virus known to cross react with MS) than the sc inoculated regressors. It is postulated, therefore, that the glass cylinder, as a privileged site conditioning tumor enhancement, leads to a decrease in immunological memory for rejection. (15 refs.)

77-5865 Rous Sarcomas in Chickens: Enhanced Growth Coexisting with Concomitant Immunity. (Eng.) McBride, R. A. (Dept. Pathology, New York Medical Coll., Valhalla, NY 10595); Watanabe, D. H.; Schierman, L. W. *Science* 197(4308): 1079-1082; 1977.

Experimental evidence shows that a second inoculation of chickens with Rous sarcoma virus (RSV), performed to demonstrate concomitant immunity, results in a marked increase in the growth rate of tumors induced by RSV 9 days earlier. Also, this increased growth rate of previously induced tumors can be demonstrated only in chickens with an intact bursa of Fabricius, even though bursectomy does not influence the expression of concomitant immunity. In addition, previously induced tumors grow more slowly in bursectomized birds given a second inoculation of RSV 9 days after the first. These results suggest that although concomitant immunity may limit the establishment and growth of metastases, it may also be a cause of more rapid growth of solid tumors that shed tumor cells into the circulation. (14 refs.)

77-5866 Murine Sarcoma Virus Pseudotypes Used as Immunogens Against Viral and Chemical Onco-

genesis. (Eng.) Basombrio, M. A. (Seccion Leucemia Experimental, Instituto de Investigaciones Hematologicas, Academia Nacional Medicina, Melo 3081, 1425 Buenos Aires, Argentina); Mayer, A. M.; Pasqualini, C. D. *Cancer Res* 37(6): 1768-1776; 1977.

Five murine sarcoma virus (MSV) pseudotypes were obtained by rescuing complete infective MSV from MSV-transformed nonproducer hamster tumor cells using the five respective murine leukemia viruses as helpers. Twenty- to 40-day-old BALB/c, C57BL/Ka, and Swiss mice were immunized with 0.2 ml of sarcoma supernatants sc and challenged 15-56 days later with oncogenic doses of sarcoma [about 0.1 to 10 TD50's (dose of MSV required to induce tumors in 50% of the mice)]. In most mice, sarcoma nodules appeared at the injection site and regressed within a month. Each pseudotype showed an individual host range pattern and, in the combinations tested, in vivo cross-reactivity could be demonstrated. The first inoculation prevented sarcoma induction by the second challenge, suggesting induction of strong immunity. Mice immunized with Rauscher and Friend MSV pseudotypes and challenged with Rauscher leukemia virus (5 LD50's) and Friend leukemia virus supernatant clearly showed a lower incidence of leukemia and longer survival. No significant difference in sarcoma incidence was observed between immunized mice and controls challenged with 32, 64, and 320 µg of 3-methylcholanthrene, implanted in the form of pellets. Thus, immunization against viral sarcomagenesis and leukemogenesis did not inhibit chemical sarcomagenesis. (19 refs.)

77-5867 **Attenuated Tumor Culture Cells Used as Immunotherapeutic Agents (Meeting Abstract).** (Eng) Eng, C. P. (Allegheny General Hospital, Pittsburgh, PA 15212); Harnaha, J. B. *In Vitro* 13(3): 158; 1977. (no refs.)

77-5868 **Effect of Systemic Administration of BCG Cell Walls on Bronchogenic Carcinoma in Hamsters.** (Eng) Zwilling, B. S. (Dept. Microbiology, Ohio State Univ., 484 W. 12th Ave., Columbus, OH 43210); Springer, S. T.; Kaufman, D. G. *J Natl Cancer Inst* 58(5): 1473-1477; 1977.

Systemic injection of BCG cell walls into Syrian hamsters was evaluated for its effects on the development of respiratory tract tumors induced by intratracheal instillation of benzo(a)-pyrene (BP) adsorbed to ferric oxide particles. Two carcinogen-treated hamster control groups had respiratory tract tumors in 76% and 72% of the animals. Only 15/29 hamsters that received one injection of BCG cell walls (300 µg) and 8/17 hamsters that received three injections of BCG cell walls had respiratory tract tumors. When only malignant tumors of the respiratory tract were considered, there was a similar reduction in the incidence in the hamsters treated with BCG

cell walls compared to controls. Both BCG treatments appeared to affect principally the late-appearing malignant tumors, since no differences were apparent in tumor incidence between BCG-treated and control groups until after the 65th week. The results cannot distinguish conclusively whether the effect of BCG cell walls was to suppress tumor development, delay tumor appearance, or both. Since this model of respiratory cancer, similarly to human lung cancer, has a long latent period, results of studies with this model may prove more relevant to the evaluation of immunoprophylaxis against lung cancer in man. (21 refs.)

77-5869 **Immunoprotection by Embryonal Carcinoma Cells for Methylcholanthrene-induced Murine Sarcomas.** (Eng) Sikora, K. (MRC Lab. Molecular Biology, Hills Road, Cambridge, England); Stern, P.; Lennox, E. *Nature* 269(5631): 813-815; 1977.

The immunization of C57BL/10ScSn mice with embryonal carcinoma cells (3 weekly sc injections of 10⁷ cells) protected the animals against subsequent challenge with methylcholanthrene (MC)-induced sarcomas (2 x 10⁵ cells, sc). The protection extended to MC tumors that did not protect against each other and to a tumor that did not protect against itself. The possibility that this cross-protection is due to antigens shared by the MC sarcomas and the embryonal carcinoma is discussed. (20 refs.)

77-5870 **In Vivo Immunomorphologic Evidence of a Specific Immune Reaction Against Virus (H.P.V.) Inducing Tumors (Warts) in Man (Meeting Abstract).** (Eng) Viac, J. (Laboratoire d'Immunopathologie, Clinique Dermatologique, Hopital Edouard Herriot, 69374 Lyon Cedex 2, France); Schmitt, D.; Thivolet, J. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 56; 1977. (no refs.)

77-5871 **Macrophage-mediated In Vitro Sensitization of T-Lymphocytes. I. Detection of Murine Leukemia Virus-Associated Antigens.** (Eng) Treves, A. J. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Medical Center, Stanford, CA 94305); Feldman, M.; Kaplan, H. S. *J Natl Cancer Inst* 58(5): 1527-1529; 1977.

The ability of mouse macrophages to sensitize T lymphocytes against RadLV, a murine leukemia virus isolated from radiogenic lymphomas of C57BL/Ka mice, and against cell cultures stably infected by the virus was tested. Three different antigenic preparations were used for feeding the macrophages: RadLV preparations from individual primary C57BL

thymomas induced by the virus; crude cell-free extracts of the disrupted cells of three cell lines [BL-5, an established line of C57BL/Ka embryo fibroblasts; BL-6(RadLV), C57BL embryo fibroblasts infected with RadLV; and R₁ leukemic cells]; and supernatants from cultures of productive BL-6(RadLV) cells. None of these antigen preparations were able to induce sensitization when applied directly to lymphocytes in vitro. When syngeneic lymphocytes were incubated with peritoneal macrophages that had been fed with crude RadLV-containing cell extracts, cytotoxic activity was observed on BL-5 and BL-6(RadLV) cells. Secondary mouse embryo fibroblasts were little affected. The supernatants from cultures of productive BL-6(RadLV) cells were immunogenic when presented to spleen lymphocytes by syngeneic macrophages. The sensitized lymphocytes were cytotoxic to BL-6(RadLV) cells and, to a lesser extent, BL-5 cells. The findings suggest that viral antigens, as well as viral-associated antigens expressed on infected cells, might be used as immunogenic entities for induction of the cell-mediated immune response in vitro. The cytotoxic lymphocytes could be used to identify these antigens on cell surfaces. (11 refs.)

- 77-5872 **In Vitro Reactivity of Macrophages and Lymphocytes from Ultraviolet-Irradiated Mice.** (Eng) Norbury, K. C. (Merck Inst. for Therapeutic Res., West Point, PA 19486); Kripke, M. L.; Budmen, M. B. *J Natl Cancer Inst* 59(4): 1231-1235; 1977.

Cultured spleen and lymph node lymphocytes from UV-irradiated inbred C3H/HeN(MTV-) (C3H-) mice did not show an impaired blastogenic response to concanavalin A, phytohemagglutinin, or lipopolysaccharide. When UV-treated mice were irradiated for 2 or 4 mo, then given thioglycollate or pyran copolymer, no differences were observed in the cell composition of peritoneal exudate cells (PEC) of test mice as compared to age-matched controls; and there was a greater number of PEC in the irradiated mice after 4 mo of UV treatment. Macrophages from these mice also showed normal phagocytic abilities toward opsonized sheep RBC. The induction of macrophage-mediated cytotoxicity was tested against the syngeneic UV-induced #2343 and #1316 fibrosarcoma cell lines, and the allogeneic B16 melanoma cell line. After mice were UV-irradiated 1 hr, 3x/wk for at least 3 mo, no in vitro reduction of tumoricidal capacity of peritoneal macrophages occurred after in vitro activation with xenogeneic lymphokines or endotoxin. It was concluded that chronic UV irradiation does not lead to a generalized immunosuppression in mice. (7 refs.)

- 77-5873 **Immune Response in Aged Mice Exposed to Lead.** (Eng) Koller, L. D. (Oregon State Univ., Sch. Veterinary Medicine, Corvallis, OR 97331); Roan, J. G.; Brauner, J. A.; Exon, J. H. *J Toxicol Environ Health* 3(3): 535-543; 1977.

B-lymphocyte, T-lymphocyte, and macrophage response were studied in CBA/J mice that had received 13 or 1,300 ppm lead in their drinking water for 18 mo, beginning at age 28 days. The immunological assays used were mitogen (lipopolysaccharide *Escherichia coli*, concanavalin A, and phytohemagglutinin-P) stimulation of lymphocytes; erythrocyte-antibody (EA), erythrocyte-antibody-complement (EAC), and phagocytosis of macrophages; and EAC of splenic lymphocytes. The low (13 ppm) of lead tended to stimulate certain immune responses (lymphocyte mitosis, EA, and EAC) but the high dose (1,300 ppm) provoked no appreciable alterations. However, these events may be obscured by the immunosuppression that normally occurs in aged mice and that may have contributed to the development of hepatic adenomas in mice exposed to 13 ppm lead and to malignant tumors (hepatocellular carcinoma and mammary sarcoma) in the 1,300-ppm group. (14 refs.)

- 77-5874 **Effect of Macrophages and Antibodies on In Vivo Growth of Moloney Sarcoma in the Rat.** (Eng) Miller, G. A. (Dept. Microbiology, Medical Coll. Virginia, Virginia Commonwealth Univ., Richmond, VA 23298); Feldman, J. D. *J Immunol* 119(4): 1445-1451; 1977.

Brown Norway (BN) and Lewis rats were challenged with a BN Moloney sarcoma tumor, MST-1, admixed with (1) nonimmune peritoneal exudate macrophages syngeneic to the host or (2) nonimmune peritoneal exudate macrophages and hyperimmune anti-MST-1 antibodies. In vivo growth of MST-1 in BN and Lewis rats was inhibited by admixing BN or Lewis macrophages, respectively, with BN anti-MST-1 antibodies. The inhibiting BN antibodies were of the IgG2 class, lacking IgG2a antibodies. BN anti-MST-1 of the IgG2 class without macrophages did not affect the growth of MST-1. BN and Lewis anti-MST IgG2a antibodies enhanced tumor growth, whether admixed with macrophages or not. Anti-MST-1 IgM and IgG1 antibodies did not influence tumor growth. Peritoneal exudate macrophages removed from Lewis donors 8-10 days after inoculation of MST-1 completely inhibited the growth of the challenge tumor; macrophages of BN origin were inhibitory only when harvested from hyperimmune donors; ie, ≥ 40 days after inoculation of MST-1. Macrophages from hyperimmune donors were specifically cytotoxic to MST-1 and did not inhibit an unrelated syngeneic BN tumor of chemical origin. (50 refs.)

- 77-5875 **Immunoglobulins in Families of Myeloma Patients.** (Eng) Festen, J. J. (Dept. Internal Medicine, State Univ. Groningen, Groningen, Netherlands); Marink, J.; de Waard-Kuiper, E. H.; Mandema, E. *Scand J Immunol* 6(9): 887-896; 1977.

With the hypothesis that a genetic predisposition to myelomatosis is related to the proliferative capacity of anti-

body-forming cells and would be reflected in the serum immunoglobulin (Ig) levels, the first-degree relatives and spouses of myeloma patients were examined for their Ig levels and the occurrence of M components. First-degree relatives of myeloma patients appeared to have higher serum levels of IgG ($p < 0.01$), IgA ($p < 0.05$), and IgM ($p = 0.02$) than their age and sex matched controls. There was no significant difference between the spouses and their controls for these parameters. Two of 325 first-degree relatives and 1/2 spouses had a serum M component but this incidence was not statistically significantly different from that of the control population. One of the relatives died of myelomatosis, which represented a frequency of this disease among first-degree relatives of myeloma patients that was significantly ($p < 0.05$) higher than that in the general Dutch population (2.8:100,000). (20 refs.)

77-5876 Cooperation of Nonsyngeneic Tolerant Lymphocytes: Genetic Restriction. (Eng) Marusic, M. (Dept. Physiology, Univ. Zagreb Faculty Medicine, Zagreb, Croatia, Yugoslavia); Goodman, J. W.; Shinpock, S. G. *Cell Immunol* 33(1): 72-80; 1977.

Genetic restrictions (ie, histocompatibility barriers to T-lymphocyte/B-lymphocyte cooperation in mounting an immune response were examined in recipient TIR (thymectomized, irradiated, reconstituted) mice made tolerant to the spleen-donor strain and vice versa. Rejection of the xenogenic rat Yoshida ascites sarcoma (YAS) tumor was the measure of successful interaction of donor T and host B lymphocytes. Fully allogeneic T and B lymphocytes did not cooperate, even when they originated from mutually tolerant animals. In the semiallogeneic combination, cell cooperation when T cells from either parent were transferred to F_1 TIR recipients, but cooperation was not observed when F_1 T lymphocytes were injected into parental C57BL/6 mice. However, when F_1 T lymphocytes were injected into P- F_1 TIR chimeras that contained exclusively parental-type lymphocytes, effective cooperation occurred, and YAS was rejected. Thus, T and B lymphocytes must share at least one major histocompatibility complex haplotype in order to cooperate. (24 refs.)

77-5877 Human Virus-infected Target Cells Lacking HLA Antigens Resist Specific T-Lymphocyte Cytolysis. (Eng) Tursz, T. (Laboratoire d'Immunohematologie et Service de Medecine, Institut Gustave Roussy, 94800 Villejuif, France); Fridman, W. H.; Senik, A.; Tsapis, A.; Fellous, M. *Nature* 269(5631): 806-808; 1977.

Human Daudi cells (from a human Burkitt's lymphoma) were resistant to lysis by Epstein-Barr virus (EBV)-sensitized T cells from infectious mononucleosis patients. The T cells were cytotoxic for histocompatibility antigen (HLA)-

positive, EBV-positive cell lines, but they were devoid of cytotoxic activity against an HLA-positive, EBV-negative line. Since Daudi cells lack HLA products, the results suggest direct HLA involvement in antiviral T-cell killing in humans. (23 refs.)

77-5878 Establishment and Characterization of a Human Epstein-Barr Virus (EBV) Negative Lymphoblastoid Cell Line Bearing Leukemia Associated Antigen(s) (Meeting Abstract). (Eng) Rosenfeld, C. (Institut de cancerologie et d'immunogenetique (INSERM), 94800-Villejuif, France); Venuat, A. M.; Choquet, C.; Goutner, A.; Kayibanda, B.; Pico, J. L.; Dore, J. F.; Greaves, M. *In Vitro* 13(3): 172; 1977. (no refs.)

77-5879 Histocompatibility Typing in Spontaneous Regression of Retinoblastoma. (Eng.) Gallie, B. L. (Wellsely Hosp., Toronto, Ontario, Canada); Dupont, B.; Whitsett, C.; Kitchen, F. D.; Ellsworth, R. M.; Good, R. A. *Prog Clin Biol Res* 16: 229-237; 1977.

The relationship of histocompatibility antigen (HLA) to the spontaneous regression of retinoblastoma was studied in 35 families with 105 unaffected and 58 affected members and in 44 retinoblastoma patients in whom family studies were not performed. The HLA typing failed to confirm either an increase in BW35 HLA antigen or a decrease in B12 antigen in retinoblastoma patients compared with healthy controls. There was a lack of association between HLA and retinoblastoma in two and three generation families. No association was found between spontaneous regression of retinoblastoma and HLA-A or HLA-B antigens in individuals or families, negating the hypothesis that a link could exist between spontaneous regression of malignant tumors and HLA antigens. (11 refs.)

77-5880 Cell-mediated Immunity to Tumor Antigen in Marek's Disease: Susceptibility of Effector Cells to Antithymocyte Serum and Enhancement of Cytotoxic Activity by *Vibrio cholerae* Neuraminidase. (Eng) Sharma, J. M. (U.S. Dept. Agriculture, Agricultural Res. Service, Regional Poultry Res. Lab., East Lansing, MI 48823). *Infect Immun* 18(1): 46-51; 1977.

Spleen cells from chickens inoculated 7-8 days previously with Marek's disease virus (10^3 plaque-forming units) were cytotoxic for ^{51}Cr -labeled cells of a Marek's disease lymphoblastoid cell line (MSB-1 line) in a 4-hr in vitro cytotoxicity assay. The cytotoxic activity of spleen cells was inhibited by pretreatment with antithymocyte serum and complement,

but not by complement alone or in combination with antitumor cell serum or normal preimmune serum. Therefore, the effector cell in the cytotoxicity assay was a T lymphocyte. Pretreatment of target cells with *Vibrio cholerae* neuraminidase enhanced the in vitro cytotoxic activity of the effector cells. Similar enzymatic treatment of effector cells had a negligible effect on cytotoxicity. (35 refs.)

- 77-5881 **Effect of Media and Passage on Generation of S₃, a Common Human Sarcoma Antigen (Meeting Abstract).** (Eng) Sethi, J. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Hirshaut, Y. *In Vitro* 13(3): 159; 1977. (1 ref.)

- 77-5882 **Antigenic Differences among Osteogenic Sarcoma Tumor Cells Taken from Different Locations in Human Tumors.** (Eng.) Byers, V. S. (Dept. Dermatology, Univ. California, San Francisco, CA 94143); Johnston, J. D. *Cancer Res* 37(9): 3173-3183; 1977.

The antigenic density on tumor cells from the center, midzone, and margin of four tumors from three patients with osteogenic sarcoma and one patient with a fibrosarcoma was determined. The tumor-associated antigen was semiquantitated by an indirect immunofluorescence assay with autologous or homologous anti-osteogenic sarcoma antisera. In all cases, the fluorescence intensity (tumor antigen density) was low on cells from the central portion of the tumor and higher on cells further from the center of the tumor and closer to the margin. Interestingly, the reciprocal relation was found when anti-HLA antiserum was used as the intermediate reactant, staining the central cells more intensely than the peripheral cells. At least some tumor antigens are suggested to be modified H-2 antigens. The central portion of the tumor was capable of specifically adsorbing antibodies directed against the midzone and margin areas of the tumor, suggesting that tumor cells from all sections share common tumor-specific antigens but differ in antigenic density. Several possible explanations for the differential gradient in antigen density are discussed, including viability, cell-cycle dependence, antigen masking or shedding, and immune selection. (37 refs.)

- 77-5883 **Tumor-associated Antigen in Bovine and Ovine Lymphosarcoma.** (Eng.) Onuma, M. (Faculty Veterinary Medicine, Hokkaido Univ., Sapporo, Japan); Olson, C. *Cancer Res* 37(9): 3249-3256; 1977.

Specific tumor-associated antigens were detected on the membrane and in the cytoplasm of lymph node cells and peripheral blood lymphocytes (PBL) from cattle and sheep

with lymphosarcoma, a lymphoproliferative disease associated with bovine leukemia virus (BLV). Among several clinically distinct forms of bovine lymphosarcoma are the common adult form (ALS) and rarer calf (CLS) and thymic (TLS) forms. Antiserum against tumor cells from ALS specifically reacted with homologous (donor) tumors by the indirect immunofluorescence test. The tumor cells in 20 lymphosarcoma cases (15 ALS, 3CLS, 2 TLS), and the PBL in the 9ALS cases tested had positive reactions to ALS antiserum, with 1% to > 30% of the cells positive. The tumor-associated antigen was detected only in the cytoplasm of fixed cells, but when living cells were examined, it was detected on the membranes. BLV was cultured from the PBL or tumor lymph nodes from 5/10 cases. ALS antiserum reacted with PBL from 1/7 BLV naturally infected and 2/7 experimentally infected cattle that had no evidence of tumor. Lymph node cells and PBL from BLV-uninfected cattle were not stained by ALS antiserum. Tumor-associated antigen was also detected in tumor cells from 5/5 sheep with lymphosarcoma using ovine lymphosarcoma (OLS) antiserum. One of seven sheep experimentally inoculated with BLV gave a positive reaction with OLS, but all four control sheep gave negative results. (25 refs.)

- 77-5884 **Immunological Selection of Tumour Cells Which Have Lost SV40 Antigen Expression.** (Eng.) Mora, P. T. (Macromolecular Biology Section, NCI, NIH, Bethesda, MD 20014); Chang, C.; Couvillion, L.; Kuster, J. M.; McFarland, V. M. *Nature* 269(5623): 37-40; 1977.

The balance between strong cellular tumorigenicity and a superimposed strong and well-characterizable [simian virus 40 (SV40)-specific] antigenic property was examined. After infection by SV40, the T-antigen-positive subclone cells of the T AL/N fibrosarcoma cell line were approx 100 times less tumorigenic than the T-antigen-negative sister subclones or the parent T AL/N clone 3 cells. When tumors from the T-antigen-positive subclones were reestablished in culture, it was found that SV40 T-, surface-, and transplantation-antigen-negative (revertant) tumor cells resulted. The experiments show that SV40 endows immunogenicity to and allows recognition and rejection of only those tumorigenic cells that are transformed by SV40; this virus may not alter the tumor-specific transplantation antigen associated with spontaneously occurring or otherwise induced malignant transformation. (23 refs.)

- 77-5885 **Biologic and Biochemical Properties of Detergent-solubilized Tumor-specific Transplantation Antigen from a Simian Virus 40-Induced Neoplasm: Brief Communication.** (Eng) Natori, T. (Lab. Cell Biology, NCI, NIH, Public Health Service, U.S. Dept. Health, Educa-

tion and Welfare, Bethesda, MD 20014); Law, L. W.; Appella, E. *J Natl Cancer Inst* 59(4): 1331-1333; 1977.

Cell membranes (CM) from dissociated ascites tumor cells from a Simian Virus 40 (SV40)-induced BALB/c mouse sarcoma were solubilized with the non-ionic detergent NP40 in order to obtain tumor-specific transplantation antigens (TSTA). Tumor rejection activity was assayed quantitatively with the use of CM, DS (detergent solubilized) fraction, and subsequent fractions I-VI obtained by gel filtration. The DS fraction (10 µg) conferred nearly 100% protection against an sc challenge 100-500 x higher than the median tumor dose of 1×10^2 mKSA cells, and a clear dose-response relationship was seen. Approx 39% of TSTA in the CM fraction was recovered in the DS fraction. TSTA was recovered in the mol wt range of 40,000-80,000 daltons. In vivo tumor rejection assays indicated that 73% of the activity found in the DS fraction was recovered in fraction V, which contained only 9% of H-2 antigen activity. The good recovery of TSTA activity obtained from CM demonstrated the effectiveness of this method for the purification and further analysis of TSTA. (14 refs.)

77-5886 Antigen-specific Purification of Blocking Factors from Sera of Mice with Chemically Induced Tumors. (Eng) Nepom, J. T. (Dept. Biochemistry, Univ. Washington Sch. Medicine, Seattle, WA 98195); Hellstrom, I.; Hellstrom, K. E. *Proc Natl Acad Sci USA* 74(10): 4605-4609; 1977.

A microcytotoxicity assay showed that serum from mice with growing tumors can prevent (block) the destruction of tumor cells by immune lymphocytes. Factors responsible for this blocking activity were purified by binding to immune adsorbents prepared from antibodies obtained by immunizing BALB/c mice to the homologous tumors. Two transplantable, methycholanthrene-induced sarcoma lines with individually different tumor-specific transplantation antigens were studied in parallel. The original tumor-specific blocking activity was recovered by elution of the immune adsorbents; ie, (a) eluates blocked the reduction of surviving tumor cell targets by immune lymphocytes only if the tumor specificity of targets and lymphocytes corresponded to the serum specificity, and (b) immune adsorbent columns prepared from tumor-immune sera recognized the purified blocking fractions in a tumor-specific fashion, indicating that a portion of the humoral response in the immune mice was directed against a factor that was individually distinct for each tumor. Absorption of eluates with the homologous tumor cells removed their blocking activity, indicating that the blocking factors have antigen-binding properties. Blocking activity in the purified fractions resided in molecules tentatively identified as glycoproteins by affinity chromatography on concanavalin A-Sepharose. (15 refs.)

77-5887 Genetics and Regulation of the Immune Response to Murine Cell-surface Antigens (Meeting Abstract). (Eng) Clark, E. A. (Univ. California, Los Angeles, CA 90024). *Diss Abstr Int [B]* 38(3): 1129; 1977. (no refs.)

77-5888 Effect of Paul Bunnell (PB) Antigen on the Spleen Focus Assay for Murine Leukemia Viruses Using Polycythemic Friend Virus (PFV) (Meeting Abstract). (Eng) Fjelde, A. (Roswell Park Memorial Inst., Buffalo, NY 14263); Evege, E. *In Vitro* 13(3): 171-172; 1977. (no refs.)

77-5889 K Cell Mediated Lysis of Cultured Colon Carcinoma and Urinary Bladder Carcinoma Cells Induced by Monospecific Antisera Against Carcinoembryonic Antigen (CEA) and Two CEA-related Normal Glycoproteins. (Eng) Hammarstrom, S. (Dept. Immunology, Univ. Stockholm, S-10691 Stockholm, Sweden); Troye, M.; Wahlund, G.; Svenberg, T.; Perlmann, P. *Int J Cancer* 19(6): 756-766; 1977.

Antibody dependent lymphocyte (K-cell)-mediated lysis of tumor cells in vitro was used as an assay for cell-surface-associated carcinoembryonic antigen (CEA) and two CEA-related normal tissue components, normal glycoprotein (NGP) and biliary glycoprotein I (BGP I). Purified normal human blood lymphocytes were used as effector cells and antibodies produced in rabbit or monkey specific for CEA of human colon carcinoma, NGP of human spleen, and BGPI from human bile as inducing agents. Target cells were (1) the CEA-containing colon carcinoma cell line HT-29, (2) a cell line from transitional cell carcinoma of the urinary bladder, T-24, and by anti-CEA. Both HT-29 and T-24 were lysed by low concentrations of anti-BGPI. Only HT-29 was lysed by anti-NGP. Although these three well-defined antigens are distributed differently on cells of different origin, they are, nevertheless, chemically and immunologically closely related. It remains to be established to what extent CEA, NGP, and BGPI are involved in the cell-mediated reactions displayed by the lymphocytes of tumor patients in the absence of added antibodies. (39 refs.)

77-5890 Detection of Tumor Specific Cytophilic Antibody in Breast Cancer Patients by Arming Guinea Pig Macrophages (Meeting Abstract). (Eng) Harris, L. F. (Northwestern Hospital, Minneapolis, MN 55407); Hickok, D. F.; Miller, L. L. *In Vitro* 13(3): 160; 1977. (no refs.)

77-5891 Detection of Antibody to Autologous Human Leukemia Cells by Immune Adherence Assays.

(Eng) Garrett, T. J. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Takahashi, T.; Clarkson, B. D.; Old, L. J. *Proc Natl Acad Sci USA* 74(10): 4587-4590; 1977.

The sera of 21 adult patients with acute leukemia were studied for the presence of antibody reacting with surface antigens of autologous leukemia cells. Sequential serum samples from patients were tested on cryo-preserved leukemia cells in immune adherence assays. Three patients showed autologous serum reactivity, and the serum of one of them was analyzed in detail. This antibody reacted with autologous acute lymphocytic leukemia cells, but not with autologous cells from peripheral blood, bone marrow, or spleen during clinical remission. In absorption tests, the antigen could not be detected on normal autologous or allogeneic blood lymphocytes, lymphoblastoid lines of T- or B-cell origin, or cells infected with simian sarcoma virus, baboon C-type virus, or Mason-Pfizer virus. Leukemia cells from two other patients with acute lymphocytic leukemia and one patient with acute nonlymphocytic leukemia absorbed specific reactivity. These studies indicate that certain acute leukemia cells express a common antigen that elicits a humoral immune response in the autologous host. (11 refs.)

77-5892 Antibodies from Healthy Cats Exposed to Feline Leukemia Virus Lyse Feline Lymphoma Cells Slowly with Cat Complement. (Eng.) Grant, C. K. (Dept. Microbiology, Harvard Univ. Sch. Public Health, 665 Huntington Ave., Boston, MA 02115); DeBoer, D. J.; Essex, M.; Worley, M. B.; Higgins, J. *J Immunol* 119(2): 401-406; 1977.

Cats exposed naturally or experimentally to feline leukemia virus (FeLV) produced antibodies that specifically lysed a feline lymphoma cell line (FL74) with cat complement (C). With homologous serum mixtures, detection of complement-dependent antibodies (CDA) in sera from FeLV-exposed cats was correlated closely, but not exactly, with detection of anti-feline oncornavirus-associated cell membrane antigen (FOCMA) in the same sera. Lysis of FL74 cells by cat antisera in the presence of cat C occurred slowly, requiring 20 hr of incubation for max effect, and a 92% correlation of CDA with anti-FOCMA was achieved. However, when heterologous rabbit or guinea pig C were used, lysis of FL74 cells by

cat antisera occurred rapidly (within 2 hr of incubation), but correlations of only 65% and 79% were achieved, respectively. Although the true significance of the slow, C-mediated lytic reaction as an immunologic effector mechanism remains unknown, these findings are consistent with the theory that antibodies to FeLV-induced cell-surface antigens play a major role in immunosurveillance in the exposed cat. (29 refs.)

77-5893 The Effects of Specific Antibody-Complement-mediated Cytotoxicity on Transformed and Untransformed Syrian Hamster Cells. (Eng.) Clarke, S. M. (Dept. Pathology, Univ. Colorado Medical Center, Denver, CO 80262); Fink, L. M. *Cancer Res* 37(9): 2985-2992; 1977.

Antibodies produced against the 220,000-mol wt proteins of Syrian hamster cells can selectively stain the surfaces and fibrillar network of untransformed Syrian hamster embryo cells. Syrian hamster embryo cells that have been neoplastically transformed by chemical carcinogens showed little or no staining. The immune antiserum, in the presence of complement, is selectively cytotoxic to the untransformed Syrian hamster embryo cells, but the transformed lines show resistance to this treatment. Sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis of lactoperoxidase-catalyzed, iodinated cell-surface proteins of the transformed lines revealed a marked reduction or absence of the 220,000-mol wt proteins, which are the major iodlatable cell-surface proteins on untransformed Syrian hamster embryo cells. Additionally, the antiserum reacts predominantly with the 220,000 mol wt protein in SDS gels. (19 refs.)

See also:

*(Rev.): 77-5424, 77-5427, 77-5432, 77-5434, 77-5441, 77-5450, 77-5451.

*(Chem.): 77-5478, 77-5482, 77-5617.

*(Phys.): 77-5664, 77-5684.

*(Viral): 77-5708, 77-5711, 77-5713, 77-5717, 77-5718, 77-5721, 77-5724, 77-5727, 77-5730, 77-5731, 77-5732, 77-5738, 77-5739, 77-5745, 77-5757, 77-5759, 77-5767, 77-5769, 77-5777, 77-5788, 77-5793, 77-5794, 77-5798, 77-5807, 77-5809, 77-5810, 77-5820, 77-5821, 77-5822, 77-5823, 77-5828, 77-5847, 77-5851.

*(Path.): 77-5896, 77-5897, 77-5905.

*(Epid.-Biom.): 77-5934, 77-5935.

PATHOGENESIS

77-5894 **Primary Abdominal Lymphoma: Presenting Manifestation of Celiac Sprue or Complicating Dermatitis Herpetiformis.** (Eng) Freeman, H. J. (Div. Gastroenterology, Dept. Medicine, Univ. Alberta, Faculty Medicine, Edmonton, Alberta, Canada); Weinstein, W. M.; Shnitka, T. K.; Piercey, J. R.; Wensel, R. H. *Am J Med* 63(4): 585-594; 1977.

Patients with celiac sprue have an increased risk of developing a primary abdominal lymphoma. The lymphoma aspect of this celiac sprue-lymphoma relationship was studied. During a 4-yr period, seven patients with abdominal lymphoma were found to have celiac sprue or a closely linked disorder, dermatitis herpetiformis. Five of the patients had a small intestinal lymphoma, one had a gastric lymphoma, and one had a retroperitoneal lymphoma. Six of the seven tumors were a diffuse histiocytic type and one was undifferentiated. In four patients, the ulcerating small intestinal lymphoma was initially diagnosed as benign ulcerative nongranulomatous jejunoileitis. In several patients the associated celiac sprue was clinically occult and could readily have been missed. The celiac sprue was fully responsive in the five patients treated with a gluten-free diet. The results suggest that celiac sprue and abdominal lymphoma occur together more often than thought. Because of the nutritional and pathogenetic implications, patients with abdominal lymphoma should be investigated for celiac sprue and dermatitis herpetiformis. (36 refs.)

77-5895 **Ultrastructural Study of Liver Sinusoids of Mice During Invasion by Leukemic Myelocytes.** (Eng) Campbell, F. R. (Dept. Anatomy, Univ. Louisville, Sch. Medicine, Health Sciences Center, Louisville, KY 40201). *J Natl Cancer Inst* 58(2): 369-376; 1977.

Electron microscopy was used to study the livers of six male RF mice 25 days after they were made leukemic by iv injection of 2×10^6 leukemic myelocytes. During the early stages of infiltration, the hepatocytes showed no signs of degeneration. The leukemic cells in the sinusoids of the liver adhered to the endothelial cells. Gaps 1-4 microns in diameter developed in the endothelium, and the leukemic cells passed through the gaps to enter the extravascular space. At a later stage of infiltration, the sinusoidal wall consisted of endothelial cells of the earlier stages, except that no permanent openings were observed. By the late stage, leukemic myelocytes were present in large numbers and few hepatocytes remained. Most of these hepatocytes showed degenerative changes. There were also fewer sinusoids, and Kupffer cells were lacking. In many of the sinusoids, which were packed with myelocytes, the endothelium had disintegrated, and the leukemia cells thus became extravascular. The occasional

openings in the endothelium were now occupied by leukemia cells migrating across the sinusoidal wall. Pores were now located within single endothelial cells, and they were smaller than the gaps used by migrating cells in earlier stages. These migration pores were approx 1 micron in diameter and were thought to be transient, since they were seen only in association with migrating myelocytes. The direction of this migration was probably from the extravascular to the vascular space, allowing the liver to function as a myelopoietic organ. (16 refs.)

77-5896 **Continuous Lymphoid Cell Line With Characteristics of "Null" Cells, Lacking the Epstein-Barr Virus Genome and Derived from Human Acute Lymphoblastic Leukaemia (Meeting Abstract).** (Eng) Kayibanda, B. (Institut de Cancerologie et d'Immunogenetique, 94800-Villejuif, France); Goutner, A.; Rosenfeld, C. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 113; 1977. (no refs.)

77-5897 **Familial Hodgkin's Disease and the Major Histocompatibility Complex.** (Eng) Bowers, T. K. (Dept. Medicine, Univ. Minnesota Sch. Medicine, Minneapolis, MN 55455); Moldow, C. F.; Bloomfield, C. D.; Yunis, E. J. *Vox Sang* 33(5): 273-277; 1977.

Major histocompatibility antigen (HLA) typing was done on 69 consecutive patients with nodular sclerosing Hodgkin's disease (HD, NS) and on 245 matched controls with the same general geographic and ethnic background. Two sisters and their immediate family were also studied in greater detail. The two siblings developed HD, NS within 3 mo of their 25th birthdays and gave identical profiles in HLA and in mixed lymphocyte culture (MLC). The HLA-B7 antigen was found in all family members. A third HLA/MLC identical sister, the mother, and the two sisters with HD, NS all shared the maternal B7 antigen but lacked the DW2 determinant; the father and a fourth sibling were heterozygous for DW2. All family members demonstrated high responses against non-DW2 cells. The presence of B7 and DW2 correlated exactly in six unrelated patients with HD, NS. For the remaining 67 patients with HD, NS, the frequencies of 23 HLA antigens did not differ significantly from the control frequencies. These results support the concept of a major histocompatibility complex-linked susceptibility to Hodgkin's disease; however, they fail to show any linkage disequilibrium with specific HLA antigens. (13 refs.)

- 77-5898 **Ph¹-positive Acute Lymphocytic Leukemia with Chromosome 7 Abnormalities.** (Eng) Mandel, E. M. (Dept. Medicine B, Res. Inst. Human Reproduction, Hasharon Hosp., Petah-Tiqva, Israel); Shabtai, F.; Gafter, U.; Klein, B.; Halbrecht, I.; Djaldetti, M. *Blood* 49(2): 281-287; 1977.

The Philadelphia chromosome (Ph¹) was present in 90% of bone marrow metaphases and 10% of peripheral blood metaphases of a 56-yr old woman with acute lymphocytic leukemia. Part of the long arm of chromosome G22 was translocated to the long arm of chromosome C9. Chromosome 7 monosomy was found in 60% of the marrow and 20% of the peripheral blood metaphases. Chromosome 7q- was also found in a small percentage of the metaphases. When the patient was in partial remission, only 10% of the marrow cells showed chromosome 7 monosomy and the Ph¹ chromosome. During complete remission, no chromosomal abnormalities were found, except for a high breakage rate. The finding of a Ph¹ chromosome in acute lymphocytic leukemia indicates that different precursors, both granulocytic and lymphocytic, may be involved in the Ph¹ process. (28 refs.)

- 77-5899 **Chromosomes and Causation of Human Cancer and Leukemia. XXVI. Banding Studies in Acute Lymphoblastic Leukemia (ALL).** (Eng) Oshimura, M. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263); Freeman, A. I.; Sandberg, A. A. *Cancer* 40(3): 1161-1172; 1977.

Karyotype analysis was performed on 101 patients with acute lymphoblastic leukemia (ALL) seen between 1968 and 1976. Over 50% of the patients (54) had abnormal chromosome numbers and/or karyotypes, while the remainder had apparently normal diploid karyotype. Two patients had a hypodiploid mode in their leukemic cells, 8 were pseudodiploid, and 23 were hyperdiploid. Twenty-one of 68 patients with normal diploid modes had some aneuploid cells in their diploid population. In 16 of 31 patients whose Q- and G-banded karyotypes were successfully completed, chromosome abnormalities were found. Four of these patients had a partial deletion of the long arm of chromosome number 6. Two of these were 6q- with additional abnormalities; and in two, 6q- was the only karyotypic abnormality. The breakpoint in this chromosome apparently involved a segment from q21 to q25. Five cases had two additional number 21 chromosomes, and two had an isochromosome of the long arm of number 7. Except for the Y chromosome, changes were observed in the chromosomes of all 16 patients. None of the patients were Ph¹-positive. Banding studies of eight patients with karyotypic instability indicated that when karyotypic evolution was present, the chromosome number increased. Thirty-seven of 42 patients were null cell, there was 1 B cell, and the 4 with abnormalities in number 6 were T cell. (18 refs.)

- 77-5900 **A Consistent Chromosome Abnormality Involving 'E' Group Chromosome in Acute Leukemias.** (Eng) Khare, A. G. (Cancer Res. Inst., Parel, Bombay-400 012, India); Advani, S. H.; Bhisey, A. N.; Ranadive, K. J. *Indian J Cancer* 14(1): 81-86; 1977.

Cytogenetic investigations were performed on five patients with acute lymphoblastic leukemia, two patients with acute myeloid leukemia (AML) and one patient with erythroblastic leukemia (EL). All patients had monosomy of the group E chromosomes; the AML patients and the EL patient were Ph¹ (Philadelphia chromosome) positive. (19 refs.)

- 77-5901 **Astrocytoma in Three Sisters.** (Eng) Pelgrom von Motz, I. (Dept. Neurology, Municipal Hosp., Leyweg 275, The Hague, Netherlands); Bots, G. T.; Endtz, L. J. *Neurology* 27(11): 1038-1041; 1977.

The case reports are presented of three sisters, aged 69, 53, and 73, each with cerebral astrocytoma. A review of the family history indicated that both the paternal and maternal sides had a higher than normal frequency of other malignancies. These cases underline the genetic and/or environmental factors involved in brain tumors. (33 refs.)

- 77-5902 **Double Minute Chromosomes and the Homogeneously Staining Regions in Chromosomes of a Human Neuroblastoma Cell Line.** (Eng) Balaban-Malenbaum, G. (Dept. Human Genetics, Univ. Pennsylvania Sch. Medicine, Philadelphia, PA 19174); Gilbert, F. *Science* 198(4318): 739-741; 1977.

Chromosome banding was used to study four human neuroblastoma cell lines (IMR-32, CHP-134, and CHP-126). All the lines contained a marked chromosome with a long nonbanding homogeneously staining region (HSR). The HSR-contained chromosome differed in each line. One line contained two classes of cells, one with an HSR marker chromosome and the other with double minute chromosomes. Each cell had one of these abnormalities, but no cell had both. The presence of two additional chromosomal markers in all cells of this line indicates a common origin. These observations suggest that the double minute chromosomes are derived from the HSR. (19 refs.)

- 77-5903 **Discussion: Genetics of Multiple Primary Tumors. A Clinical Etiologic Approach Illustrated**

y Three Patients. (Eng) Mulvihill, J. J. (Landow Building, Room A521, NCI, Bethesda, MD 20014); McKeen, E. A. *Cancer [Suppl]* 40(4): 1867-1871; 1977.

linicians can shed new light on the genetic and environmental origins of cancer, particularly multiple primary malignancies, by asking additional questions at the bedside. Areas to explore include occupational history, personal habits, residence, and medical and family histories, with emphasis on subtle clues of disorders predisposing to cancer, such as birth defects and benign neoplasms. When this bedside approach to cancer etiology was applied to three patients with a total of 19 primary malignancies, the striking finding was the variety of benign neoplasms in the patients and a similar array of benign and malignant tumors among their first-degree relatives, some of whom also had multiple primary tumors. A single gene trait, Cowden's (multiple hamartoma) disease, was recognized in one patient. In future studies of multiple tumors, epidemiologists should consider not only malignancies, but all forms of neoplasia, in patients and their families. (5 refs.)

77-5904 **Role of Heredity in Multiple Primary Cancer.** (Eng) Lynch, H. T. (Dept. Preventive Medicine/Public Health, Creighton Univ., 2500 California St., Omaha, NB 68178); Harris, R. E.; Lynch, P. M.; Guirgis, J. A.; Lynch, J. F.; Bardawil, W. A. *Cancer [Suppl]* 40(4): 1849-1854; 1977.

The occurrence of multiple primary malignant neoplasms was examined in 11 families with the cancer family syndrome heritable adenocarcinomas of the colon and endometrium) and a single extended kindred with site-specific colon cancer. Of the 316 relatives with cancer in the 12 families, 68 had two or more primary malignancies and 59 of these multiple primaries involved the colon and/or endometrium. A pooled analysis of the data revealed a consistent 3% risk for a second primary cancer in each year of survival following first onset. If a second primary occurs, the risk for a third is extremely high (6.9%/yr), but it shows a nonlinear trend with increasing survival following second onset. The high risk of extraprimaries malignancies in patients from these kindreds indicates that careful consideration should be given to the total removal of principal target organs following the initial manifestation of cancer. (13 refs.)

77-5905 **Two-Step Chromosomal Control of Tumorigenicity of Chinese Hamster Cells in Nude Mice.** (Eng) Ebina, T. (Dept. Bacteriology, Tohoku Univ. Sch. Medicine, 2-1 Seiryomachin, Sendai 980, Japan); Imai, M.; Ishida, N. *Int J Cancer* 20(4): 572-580; 1977.

A simple method for microinjecting isolated chromosomes to a single living cell under an inverted microscope is de-

scribed. Of 368 injected cells, 85 were able to form a colony and could be cloned. Clones of Chinese hamster V79 cells microinjected with chromosomes from murine D56 cells [V79(D56) cells] were tested for tumorigenicity in immunodeficient nude mice and for colony-forming ability in soft agar. Untreated recipient V79 cells were highly tumorigenic and had a high colony-forming ability in soft agar. In contrast, 2/21 microinjected clones tested were nontumorigenic in nude mice and had only weak colony-forming ability in soft agar. The chromosome banding pattern was analyzed in microinjected clones and tumors derived from cells of these clones. In cells of the two nontumorigenic clones, a telocentric chromosome 1 (t1) was specifically involved in translocations with other chromosomes or chromosome fragments. In all tumor cells from nude mice, a supernumerary piece or a whole banded chromosome 14(b14) was found. The results suggest that the t1 chromosome bears the gene that controls in vitro transformation and that the additional genetic change, ie, the extra piece of b14 chromosome, was required for tumor formation in vivo. (23 refs.)

77-5906 **Fully Characterized Cultured Cell Lines from Human Tumors (Meeting Abstract).** (Eng) Fogh, J. (Walker Lab., Sloan-Kettering Inst. for Cancer Res., Rye, NY 10580); Fogh, J. M.; Fogh, H.; Loveless, J.; Milder, D.; Wright, W. *In Vitro* 13(3): 175; 1977. (no refs.)

77-5907 **Chromosome 1 in Cervical Carcinoma (Letter to Editor).** (Eng) Atkin, N. B. (Dept. Cancer Res., Mount Vernon Hosp., Northwood, Middlesex HA6 2RN, England); Baker, M. C. *Lancet* 2(8045): 984; 1977.

Abnormalities in chromosome number 1 were detected in 14 consecutive near-diploid carcinomas of the uterine cervix. Five of these exhibited trisomy of this chromosome. It is suggested that there is a relationship between heteromorphism for the heterochromatic region of chromosome number 1, pericentric inversion of this region, and an increased risk of cancer. (5 refs.)

77-5908 **Marker Chromosome(s) in Cell Lines Established from Primary and Metastatic Human Breast Carcinomas (Meeting Abstract).** (Eng) Pathak, S. (Dept. Biology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Cruciger, Q.; Farris, T.; Cailleau, R. *In Vitro* 13(3): 199; 1977. (no refs.)

77-5909 **Chromosome Replication Patterns in Heteroploid Rat Sarcoma Cells in Primary Culture**

(Meeting Abstract). (Eng) Sklarew, R. J. (New York Univ. Res. Service, Goldwater Memorial Hosp., Roosevelt Island, New York, NY 10044); Hoffman, J.; Post, J. *In Vitro* 13(3): 200; 1977. (2 refs.)

77-5910 **Personal Observations Concerning Premalignant and Malignant Lesions of the Body of the Uterus.** (Fre) Uyttenbroeck, F. (No affiliation given). *Chirurgie* 103(2): 122-129; 1977.

The symptomatology and the results of treatment of 241 women with premalignant (92 patients) or malignant (149) lesions of the endometrium are presented. Four patients had an intraepithelial cancer, and 29 had both malignant and premalignant lesions. Overall, 221 of the patients were in menopause and 20 had attained sexual maturity. Of the patients with malignancies 4 were in Stage 0, 136 in Stage I, 2 in Stage II, 8 in Stage III, and 3 in Stage IV disease. The myometrium was affected in 103 patients; 134 patients had an adenocarcinoma, 3 adenoacanthoma, 5 sarcoma, 4 anaplastic cancer, 1 malignant adenoma, and 1 an epidermoid epithelioma. Four patients had metastases to one or both ovaries, 3 had another malignancy, and 14 had benign tumors of the ovaries. Metrorrhagia was the main symptom in 139 of the patients. Hysterectomy was performed in patients with precancerous conditions provided that the lesion was not estrogen-induced. Patients with malignancies had a total hysterectomy, with removal of the adnexae followed by telecobalt therapy. The 5-yr survival rate of all patients with malignancies was 67.35%. Of the 54 patients who died, 38 died within 5 yr, 16 died 5 yr after surgery, and 9 died 10 yr after surgery. Survival was longer if the myometrium was not affected. Overall, 32/241 patients had been taking estrogens and synthetic progestagens. Postmenopausal active glandulocystic hyperplasia was found frequently in patients taking estrogens. Five patients who had endometrial cancer had taken estrogens. (no refs.)

77-5911 **In Vitro Growth Patterns of the Human Uterine Cervix, Benign & Malignant (Meeting Abstract).** (Eng) Wilbanks, G. D. (Rush Presbyterian St. Luke's Medical Center, Chicago, IL 60612). *In Vitro* 13(3): 144; 1977. (no refs.)

77-5912 **Neurilemmoma-like Uterine Myomas: An Ultrastructural Reaffirmation of Their Non-Schwannian Nature.** (Eng) Gisser, S. D. (Albert Einstein Medical Center, York and Tabor Roads, Philadelphia, PA 19141); Young, I. *Am J Obstet Gynecol* 129(4): 389-392; 1977.

Some uterine leiomyomas demonstrate a rhythmic pattern of cellular arrangement that is suggestive of nerve sheath tumors. Leiomyomas with a similar appearance are more frequent in the gastrointestinal tract. An ultrastructural examination of two uterine leiomyomas, one simulating the Antoni type A pattern and the other the Antoni type B pattern, revealed features of smooth muscle cells in each tumor. There was also a close structural resemblance to the microscopic appearance of similar tumors of the gastrointestinal tract. This study should dispel the implications that these tumors are of Schwannian origin. (8 refs.)

77-5913 **Adenomyoma: A Precursor of Extrauterine Mullerian Adenosarcoma.** (Eng) Mahoney, A. D. (Dept. Pathology, Loma Linda Medical Center, Loma Linda, CA); Waisman, J.; Zeldis, L. *J. Arch Pathol Lab Med* 101(11): 579-584; 1977.

A case report is presented for a 55-yr-old woman with an extrauterine pelvic mullerian adenosarcoma that recurred on multiple occasions and that was originally diagnosed as a benign lesion. Caution is needed in the initial interpretation of these lesions as adenofibromas. The focal cellularity, frequency of mitotic figures, and subsequent behavior of the tumor were indicative of a low-grade malignancy, which may have arisen from a pelvic adenomyoma rather than an endometriotic lesion. A comparison of this lesion with a benign uterine adenomyoma from a 22-yr-old patient suggested that such benign tumors could be precursors of some mullerian adenosarcomas. (8 refs.)

77-5914 **Yolk Sac Derived Teratoma and Carcinoma in Hamsters.** (Eng) Sobis, H. (Rega Inst., Univ. Leuven, B-3000 Leuven, Belgium); Vandeputte, M. *Eur J Cancer* 13(10): 1175-1181; 1977.

The induction and the histology of visceral yolk sac-derived benign teratomas in hamsters are described. The teratomas are characterized by the presence of adult well-differentiated tissues from all three germ layers. In these teratomas, malignant transformation to yolk sac carcinoma was occasionally observed. The histogenesis of this malignant tumor is described, and its origin is discussed in relation to virus induced yolk sac carcinoma. (28 refs.)

77-5915 **Explant Culture of Normal and Tumor Bearing Human Prostate Glands (Meeting Abstract).** (Eng) Claflin, A. J. (Univ. Miami School of Medicine, Miami, FL 33152); Malinin, T. I.; Block, N. L. *In Vitro* 13(3): 179; 1977. (no refs.)

-5916 **Primary Carcinoma of the Male Urethra Developing after Urethroplasty for Stricture.** (Eng) Lapinto, V. (170 St. George St., Suite 724, Toronto, Ontario, Canada); Evans, D. H. *J Urol* 118(4): 581-584; 1977.

A 67-yr-old man developed squamous cell carcinoma of the urethra 4 yr after urethroplasty for stricture. Two similar cases from the literature are reviewed. These malignancies could result from unrecognized carcinoma at urethroplasty, progression of squamous metaplasia to malignancy, chronic irritation giving rise to malignancy, or carcinoma arising from the skin flaps of the urethroplasty. (12 refs.)

-5917 **Ultrastructural Observations of the So-called Strumal Carcinoid of the Ovary.** (Eng) Livnat, J. (Dept. Obstetrics and Gynecology, Michael Reese Hospital and Medical Center, 29th and Ellis Sts., Chicago, IL 60616); Gommemma, A.; Recant, W.; Jao, W. *Arch Pathol Lab Med* 1(11): 585-589; 1977.

A strumal carcinoid arose in a benign cystic teratoma of the ovary. Ultrastructural studies demonstrated that both the solid and acinotubular areas as well as the follicular components are composed of light and dark cells that contained numerous secretory granules. These findings indicate that this neoplasm was pure carcinoid tumor with a follicular pattern. This study raises the question of whether all strumal carcinoids are indeed pure carcinoid neoplasms. (24 refs.)

-5918 **Estrogen and Progestogen Cytosol Receptors in Human Breast Carcinoma.** (Fre.) May-Levin, F. (Institut Gustave-Roussy, 94800 Villejuif, France); Guerinet, L.; Contesso, G.; Delarue, J. C.; Bohuon, C. *Int J Cancer* 21(6): 789-795; 1977.

Estrogen (ES) and progestogen (PR) cytosol receptors were determined in 379 breast carcinoma samples from 281 primary operable tumors, 26 pseudoinflammatory tumors, 52 metastases, and 20 recurrences. An exchange technique using ³H-radiol for ES and R5020 (a synthetic compound) for PR was used for the assay. Of the operable cases, 77/164 tumors with anaplastic histology possessed both ES and PR receptors, compared with 16/63 tumors with an atypical histology. Furthermore, 26/53 Stage I tumors had both receptors, as did 35/98 Stage III tumors. Postmenopausal patients had a high ES level but a low PR level, whereas premenopausal patients had a high PR level and a low ES level. Overall, 32% of the 281 operable patients had no receptors if tumors are considered receptor-positive when the binding site concentration exceeds 100 femtomoles/g tissue. Both receptors were found in 54% of the patients, ES only in 31%, and PR only in 15%. A relatively high proportion of the 26 patients with pseudoinflammatory tumors had neither receptor, and only 1/20 with recurrence had both receptors. However, 54% of the 60 patients with metastases had both receptors. (22 refs.)

77-5919 **In Vivo Initiated Rat Liver Carcinogenesis Studied In Vitro; Formation of Alcoholic Hyaline-type Bodies.** (Eng.) Borenfreund, E. (Lab Cell Biochemistry, Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Higgins, P. J.; Bendich, A. *Cancer Lett* 3(3-4): 145-150; 1977.

Female Wistar rats had continuous access to drinking water containing diethylnitrosamine (DEN: 5 mg/100 ml). After 10-14 wk, the liver cells that showed hepatocellular carcinoma were propagated in culture for about 2 mo. The cells were epithelioid in appearance and occasionally showed acentrically displaced nuclei. The hyaline areas were about the same size as the nuclei, and they stained red with Mallory phosphorin and blue with Cason's modification of the Mallory stain, as described for Mallory bodies in cirrhotic livers. The morphologic changes and disarrayed filaments in these hyaline-type bodies were retained on serial passages for many months. Cells injected into nude mice or newborn rats produced carcinomas from which cells with these abnormalities were reestablished in continuous culture. (38 refs.)

77-5920 **The Initiation-Selection-Cancer Sequence in the Pathogenesis of Hepatocellular Carcinoma (Meeting Abstract).** (Eng) Medline, A. (Dept. Pathology, Univ. Toronto, Toronto, Canada); Ogawa, K.; Solt, D.; Farber, E. *Gastroenterology* 73(5): 1234; 1977. (no refs.)

77-5921 **Benign Liver-Cell Adenoma Associated with Long-Term Administration of an Androgenic-Anabolic Steroid (Methandienone).** (Eng) Hernandez-Nieto, L. (Escuela de Hematologia, Hospital Clinico Y Provincial, Casanova, 143, Barcelona-11 Spain); Bruguera, M.; Bombi, J. A.; Camacho, L.; Rozman, C. *Cancer* 40(4): 1761-1764; 1977.

A 19-yr-old man with paroxysmal nocturnal hemoglobinuria treated for 3 yr with Methandienone was admitted with hemoperitoneum due to rupture of a hepatic tumor. Histological examination revealed a benign liver cell adenoma that closely resembled hepatic tumors associated with contraceptive steroids. (29 refs.)

77-5922 **Scanning Electron Microscopic Surface Morphology of Isolated Hepatocytes from Normal and Premalignant Rat Liver.** (Eng.) Boman, D. (Zoological Inst., Univ. Oslo, Oslo, Norway); Berg, T.; Christoffersen, T. *Acta Pathol Microbiol Scand [A]* 85(4): 481-488; 1977.

Scanning electron microscopy was performed on hepatocytes isolated after collagenase perfusion of livers from normal rats and from rats fed 2-acetylaminofluorene (AAF, 0.025%) in the diet for 6-8 wk. The cells from the AAF-treated rats varied more in size and exhibited a more irregular shape than the normal cells. They also had less than half

the number of microvilli and 4 times more protrusions and blebs than normal hepatocytes. The microvilli of the control cells were regular and situated on an even surface, but the irregular microvilli of the AAF hepatocytes seemed to protrude from a more ruffled surface. Livers from AAF-treated rats have increased levels of cyclic AMP compared with controls. It is suggested that the reduced number of microvilli observed on the hepatocytes from AAF-treated rats might be consistent with an inverse relationship between cyclic AMP level and the number of microvilli. (24 refs.)

- 77-5923 Multinucleated Giant Cell Neoplasm of Pancreas: Light and Electron Microscopy Features.** (Eng) Robinson, L. (Dept. Pathology, Univ. Alabama Medical Center, Birmingham, AL 35294); Damjenov, I.; Brezina, P. *Arch Pathol Lab Med* 101(11): 590-593; 1977.

The morphological features, demonstrated by electron microscopy, of a rare pancreatic neoplasm indistinguishable from giant cell tumor of bone by light microscopy are presented. These findings are compared with those of the only other reported case studied by electron microscopy. Features were noted in both studies that are strongly suggestive of the epithelial origin of this neoplasm. However, the multinucleated giant cells and the B-type mononuclear cells in the present case were very similar to the corresponding cells of giant cell bone tumors. The degree of differentiation seems to be the most likely determinant of the degree of similarity of the pancreatic neoplasm to the skeletal lesion. (7 refs.)

- 77-5924 Ultrastructure of the Mesothelioma of the Atrioventricular Node.** (Eng.) Fenoglio, J. J. (Dept. Cardiovascular Pathology, Armed Forces Inst. Pathology, Washington, DC 20306); Jacobs, D. W.; McAllister, H. A. *Cancer* 40(2): 721-727; 1977.

Two tumors of the atrioventricular node (conduction tumors) were examined by electron microscopy to determine their histogenesis. Ultrastructurally, the tumors were composed of nests of cells arranged in small channels and tubules set in a connective tissue stroma. The cells lining the tubules were flattened or low cuboidal and had abundant microvilli over the lumen surface. The cells were joined by specialized junctions along their lateral adjacent borders, especially at the luminal surfaces, and intercellular spaces delineated by specialized junctions were frequent. Microvilli, intercellular spaces bounded by tight junctions, and complex intercellular junctions are features of mesothelial cells as well as of benign mesotheliomas of the genital tract. The ultrastructural similarity of the conduction tumors to mesotheliomas and the absence of structures suggestive of an epithelial or endothelial origin led to the conclusion that the conduction tumor is derived from mesothelial cells. The findings support a previous theory that these tumors are mesotheliomas of the atrioventricular node and are probably derived from cells of the mesothelial covering of the embryonic heart that are trapped

in the atrial septum, often in the region of the atrioventricular node, as the embryonic heart folds on itself during development. (14 refs.)

- 77-5925 Ultrastructure of Malignant Fibroxanthoma.** (Rus) Galil-Ogly, G. A. (Moscow Scientific Res. Inst. Roentgenology and Radiology, Ministry Public Health RSFSR, Moscow, USSR); Krylov, L. M.; Poroshin, K. K. *Arkhh Patol* 39(6): 42-48; 1977.

Electron microscopy studies of malignant fibroxanthomas surgically removed from two women aged 52 and 62 yr are described. Histiocyte- and fibroblastlike cells and cells with a low degree of differentiation were distinguished among the tumor elements. The histiocytelike cells were the most numerous. They had round or oval nuclei, a cytoplasm with a well-developed Golgi complex, usually in the perinuclear zone, and many cytoplasmic processes of varying shapes. The fibroblastlike cells had elongated or irregular nuclei with large nucleoli, long cytoplasmic processes, and, usually, a smooth cell surface. Cells with a low degree of differentiation had round or oval nuclei and an underdeveloped cytoplasm of low electron density, with scattered ribosomes, small vesicles, dense bodies, and cytoplasmic filaments. Some of these cells showed signs of macrophage differentiation, which suggested the possibility of their transformation into histiocytes. It was not possible to establish any relationship between these barely differentiated cells and fibroblastlike cells. (11 refs.)

- 77-5926 A Typical Cutaneous Fibroxanthoma Undergoing Malignant Transformation. Report of a Case Studied Electron Microscopically and in Tissue Cultures (Meeting Abstract).** (Fre) de Saint-Maur, P. P. (No affiliation given); Lecomte, D.; Taillemite, J. L.; Krulik, M.; Mougeot-Martin, M. *Arch Anat Cytol Pathol* 25(3): 214-215; 1977. (no refs.)

See also:

- * (Rev.): 77-5405, 77-5406, 77-5424, 77-5430, 77-5431, 77-5433, 77-5434, 77-5435, 77-5436, 77-5438, 77-5439, 77-5440, 77-5441, 77-5442, 77-5443, 77-5444, 77-5445, 77-5446, 77-5447, 77-5448, 77-5449, 77-5451, 77-5452, 77-5453, 77-5454, 77-5455, 77-5458.
 * (Chem.): 77-5490, 77-5497, 77-5518, 77-5524, 77-5526, 77-5527, 77-5530, 77-5547, 77-5571, 77-5575, 77-5589, 77-5594, 77-5595, 77-5598, 77-5615, 77-5621, 77-5624, 77-5630, 77-5635, 77-5638, 77-5639, 77-5640, 77-5642, 77-5645.
 * (Phys.): 77-5653, 77-5654, 77-5656, 77-5667, 77-5669, 77-5672, 77-5689, 77-5690, 77-5692, 77-5696.
 * (Viral): 77-5698, 77-5783, 77-5797, 77-5798, 77-5803, 77-5819, 77-5825, 77-5844, 77-5848.
 * (Immun.): 77-5858, 77-5859, 77-5875, 77-5882.
 * (Epid.-Biom.): 77-5929, 77-5930, 77-5935, 77-5936, 77-5959, 77-5962.

EPIDEMIOLOGY AND BIOMETRY

- 77-5927 **Carcinoma of the Cervix Uteri in Ibadan: Coital Characteristics.** (Eng) Adelus, B. (Dept. Obstetrics and Gynecology, Univ. Ibadan, Ibadan, Nigeria). *Int J Gynecol Obstet* 15: 5-11; 1977.

The role of coitus in the incidence of cervical cancer was studied in 114 Nigerian women with a histologic diagnosis of invasive carcinoma of the cervix; 36 women with cervicitis, cervical erosion, or cervical warts; and 106 healthy women of childbearing age. A significantly greater percentage of the carcinoma group (31.6%) than that of the control group (10.4%) commenced sexual activity early in life (11-15 yr of age). Of those women with cervical cancer 35.1% had been married at least twice, but only 18.8% of the healthy controls had had two or more partners. A significantly higher proportion of the control group had coitus less than three times per week (81.4% vs 62.9% in the carcinoma group and 57.6% in the cervicitis group), and a significantly higher proportion of the carcinoma group (56.1% vs 37.8% in controls) had six or more pregnancies. Coitus thus appears to be the common denominator that can explain the occurrence of cervical cancer among women who engage in early sexual practice, have intercourse frequently and with multiple sexual partners, and have many pregnancies. The possibility of a sexually transmitted factor is suggested. (27 refs.)

- 77-5928 **"Pap" Testing and Hysterectomy Prevalence: A Survey of Communities with High and Low Cervical Cancer Rates.** (Eng) Stern, E. (Div. Epidemiology, Sch. Public Health, Univ. California, Los Angeles, CA 90024); Mischynski, M.; Greenland, S.; Damus, K.; Coulson, A. *Am J Epidemiol* 106(4): 296-305; 1977.

Areas of Los Angeles County with high and low rates of cervical cancer were surveyed in an attempt to relate these rates to the level of Papanicolaou (Pap) screening and prevalence of hysterectomy. There was an inverse relation between cervical cancer rates and income and a positive association between level of Pap testing and income. Ethnic differences in cervical cancer rates and Pap testing depended on income. The relatively high rate of cervical cancer and low level of systematic screening in low-income communities suggest that a community trial to assess the value of cytologic screening in reducing cervical cancer rates is feasible. Information on hysterectomy prevalence by type of procedure supports the idea that the long-observed decline in cervical cancer rates is partly due to a concomitant decrease in the ratio of subtotal to total hysterectomy. (10 refs.)

- 77-5929 **Mammographic Parenchymal Patterns and the Prevalence of Breast Cancer.** (Eng) Peyster, R.

G. (Dept. Radiology, Massachusetts General Hosp., Boston, MA 02114); Kalisher, L.; Cole, P. *Radiology* 125: 387-391; 1977.

The relationship between breast parenchymal patterns and breast cancer prevalence in a large referral population was investigated. Mammograms were assigned to one of four categories according to Wolfe's classification for 402 breast cancer cases and 1,036 controls. Cancer prevalence for the four patterns was similar when uncorrected for age, and it was very high compared to that in the general population. Under age 50, the prominent duct pattern (P₂) was associated with a very high relative cancer risk; the dysplastic pattern carried a smaller increased risk. After age 50, prevalences for the patterns were nearly equal. The relationship between these findings and the epidemiology of breast cancer are discussed, and suggestions are made for utilizing parenchymal patterns to guide examination frequency. (6 refs.)

- 77-5930 **Bilateral Primary Breast Cancer Treated at the Cancer Institute Hospital, Tokyo.** (Eng.) Fukami, A. (Dept. Surgery and Pathology, Cancer Inst. Hosp., Tokyo, Japan); Kasumi, F.; Hori, M.; Kuno, K.; Kajitani, T.; Sakamoto, G.; Sugano, H. *Prog Clin Biol Res* 16: 525-535; 1977.

Between 1965 and 1975, 3,365 women with breast carcinoma were treated in the Cancer Institute Hospital, Tokyo. Bilateral carcinoma was found in 104 patients, and, of these, 94 developed a clinically defined primary carcinoma in the second breast and 10 developed metastatic lesions. Ninety-two of the 94 patients with primary carcinomas were studied. Of these, 69 cases were asynchronous and 23 were synchronous. A family history of breast carcinoma was present in 13/92 of the patients with primary lesions, a rate significantly higher than that in patients with unilateral breast carcinoma. The percentage of patients with nodal involvement at the time of the first cancer was 37.3. At the time of the second cancer development, the percentage with nodal involvement was 28. The highest incidence of bilateral breast cancer was found in patients without metastases to the lymph nodes. Women with mucinous, scirrhous, papillotubular, and tubular medullary carcinoma were more likely to develop cancer in the other breast than those with other types. The overall incidence of bilateral breast cancer (104/3,365) was two to three times less than that in US women. (9 refs.)

- 77-5931 **Left-sided Breast Cancer (Letter to Editor).** (Eng.) Blot, W. J. (Environmental Epidemiology and Biometry Branches, NCI, Bethesda, MD 20014); Fraumeni, J. F.; Young, J. L. *Lancet* 2(8041): 762-763; 1977.

Studies of the incidence of left- and right-sided breast cancers have indicated a 6% excess of left-sided tumors, primarily in peri- and postmenopausal women. However, if this were due to genetic factors, the ratio of left to right breast cancers would be greater in younger women. Thus, these findings in older patients appear to reflect environmental influences. (6 refs.)

- 77-5932 **Geographic Patterns of Breast Cancer in the United States.** (Eng) Blot, W. J. (Environmental Epidemiology Branch, NCI, NIH, Public Health Service, U. S. Dept. Health and Education, Welfare, Bethesda, MD 20014); Fraumeni, J. F.; Stone, B. J. *J Natl Cancer Inst* 59(5): 1407-1411; 1977.

The geographic variation of breast cancer across the US was studied by calculating the correlations between mortality rates for premenopausal and postmenopausal women and demographic, socioeconomic, and ethnicity data for the 3,056 US counties. The demographic indicators of high mortality from breast cancer for women 20-44 yr old were (in order of magnitude of their standardized regression coefficients): (1) urbanization, (2) low birth rate, and (3) high ovarian cancer mortality. For women > 55 yr old, the indicators were: (1) regional location (highest rates in the Northeast), (2) high income, (3) German descent, (4) high colon cancer mortality, (5) urbanization, (6) high ovarian cancer mortality, (7) low birth rate, (8) Scandinavian descent. The role of reproductive and endocrine determinants was discussed. It might account for the associations of breast cancer mortality with ovarian cancer mortality and low birth rates. Other evidence has suggested the role of diet in the genesis of breast cancer. Although ethnic, urban, socioeconomic, and fertility patterns influence breast cancer mortality, these factors cannot fully account for the geographic variations. (22 refs.)

- 77-5933 **An Association Between ABO Blood-Group Distribution and Geographic Differences in Death-Rates.** (Eng) Mitchell, J. R. (Univ. Dept. Medicine, General Hosp., Nottingham NG1 6HA, England). *Lancet* 1(8006): 295-297; 1977.

Studies of the relation between blood-group and death rates in England, Wales, and Scotland revealed the weakest correlation for bronchial neoplasms and the strongest for arteriosclerotic and coronary heart-disease in the men. In the women breast carcinoma showed no correlation with blood type, whereas vascular disease of the CNS and heart-disease did. (25 refs.)

- 77-5934 **Comparative Studies on Immunity to EBV-associated Antigens in NPC Patients in North**

America, Tunisia, France and Hong Kong. (Eng.) Levine, P. H. (Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD 20014); Wallen, W. C.; Ablashi, D. V.; Granlund, D. J.; Connelly, R. *Int J Cancer* 20(3): 332-338; 1977.

Following the hypothesis that Epstein-Barr virus (EBV) is etiologically related to nasopharyngeal carcinoma (NPC), the relative antibody titers to EBV-related antigens in NPC patients and controls from a high-incidence (Hong Kong), an intermediate incidence (Tunisia), and two low-incidence (France, North America) areas were determined. The EBV antibodies measured include anti-virus capsid antigen (VCA), anti-early antigen (EA), anti-soluble antigen by complement-fixation (CF) and antibody-dependent lymphocyte cytotoxicity (ADLC) assays. A matched-pair analysis showed that significantly more NPC patients had higher VCA and EA but not CF or ADLC antibody titers than their matched controls (patients with other carcinomas). Comparison of the geometric mean titers revealed that the differences between NPC cases and controls were more than sevenfold (81.6 vs 11.5) for EA and more than threefold (359.7 vs 95.4) for VCA, both highly significant ($p < 0.001$). A twofold difference was observed for CF (27.3 vs 12.9, $p < 0.01$) and a threefold difference was seen for ADLC (2,657.7 vs 870.9, $p < 0.05$). These findings suggest that if EBV is the etiologic agent of NPC in the Chinese, it is likely to cause the majority of NPC cases in other ethnic groups living in other countries as well. (29 refs.)

- 77-5935 **HLA and Nasopharyngeal Cancer.** (Eng.) Simons, M. J. (WHO Immunology and Training Center, Univ. Singapore, Singapore); Chan, S. H.; Day, N. E.; Wee, G. B.; Shanmugaratnam, K. *Prog Clin Biol Res* 16: 145-148; 1977.

The genetic and immunologic bases of susceptibility to nasopharyngeal cancer (NPC) were studied in southern Chinese and Malay patients possessing the histocompatibility (HLA) haplotypes. The age-standardized differential incidence of NPC was found to vary between the Cantonese, Hokkien, and Teochew dialect groups (29.4, 13.7, and 14.4/10⁵ in men and 10.8, 4.4, and 5.9/10⁵ in women) and was also reflected in the A2-Sin 2 antigen frequency in these three groups. The frequency of A2-Sin 2 was lower in long-term Chinese survivors than in newly diagnosed cases, suggesting that this haplotype is also associated with the chance of survival. In Malay patients, NPC was associated with the A9-B18 haplotype. Both HLA haplotypes were in linkage-disequilibrium in the respective normal populations and in even greater disequilibrium in NPC patients. This supports the hypothesis that the high risk of NPC among southern Chinese stems from the presence of disease susceptibility (DS) genes associated with the HLA haplotypes. The authors suggest that due to the close association between NPC and Epstein-Barr virus (EBV), the DS gene might also be involved in the immune response to EBV. (9 refs.)

77-5936 **Families with Multiple Cases of Urinary System Tumors: Brief Communication.** (Eng) Petrova-Pacharova, T. (Inst. Oncology, Medical Acad., Sofia, 1156, Bulgaria); Chernozemsky, I. N.; Nikolov, I. G.; Stoyanov, I. *J Natl Cancer Inst* 59(5): 1419-1421; 1977.

A study was made of three families living in different villages with endemic nephropathy (EN) in Vratza, Bulgaria. Among 71 family members > 30 yr old, 9 had urinary system tumors (UST), 7 had UST and EN, and 7 had EN. Most of the cases had been registered between 1962 and 1976, and the patients were 40-60 yr old. Transitional cell carcinoma of the kidney, pelvis, ureter, and urinary bladder were found most frequently, with often more than one site in the urinary system being involved. Persons related by marriage and coming from nonendemic families and villages were affected by both diseases. Although descendants of brothers and sisters of the first generations of the three families, who live in neighboring villages or in the same village but in other households greatly outnumber the study group, only one case of EN and no cases of UST have been registered. Although this report provided an example of familial aggregation of cancer of single system, the causal relationship of genetic and/or environmental factors remains unknown. (16 refs.)

77-5937 **Results of a One-Year Epidemiological Survey on Cancer of the Digestive Tract in the Gold Coast (Meeting Abstract).** (Fre) Faivre, J. (Centre d'Hepato-gastro-Enterologie, Hopital General, CHU, Dijon, France); Faivre, M.; Legoux, J. L.; Cueugnet, C.; Martin, F.; Michiels, J.; Dusserre, P.; Cabanne, F.; Klepping, C. *Gastroenterol Clin Biol* 1(5): 483-484; 1977. (no refs.)

77-5938 **Factors Related to the Incidence of Stomach Cancer in the Pittsburgh Standard Metropolitan Statistical Area.** (Eng) Lerer, T. J. (Dept. Biostatistics, 8 Parran Hall, Graduate Sch. Public Health, 130 DeSoto Ave., Univ. Pittsburgh, Pittsburgh, PA 15261); Redmond, C.; Campbell, J. *J Natl Cancer Inst* 59(4): 1065-1071; 1977.

Several demographic discriminants of stomach cancer incidence for residents of the Pittsburgh Standard Metropolitan Statistical Area were analyzed with the use of data collected in the Third National Cancer Survey, 1969-1971. In the survey, Pittsburgh residents showed the highest age-adjusted incidence rate for stomach cancer and the fifth highest rate for all sites. Sex, race, country of origin, and median income level were used to classify the cancer patients into homogeneous subgroups of census tracts of residence, which permitted comparisons of the average annual age-adjusted incidence rates among the groups. The data indicated that Pittsburgh residents had stomach cancer incidence patterns that were generally consistent with earlier published reports. When contrasted with appropriate population subgroups, higher rates

appeared for men, blacks, lower-income areas, and areas with "large" proportions of foreign-born and foreign-stock residents. Furthermore, the relationship between ethnic composition and incidence appeared to supercede that of income among white men. (44 refs.)

77-5939 **The Possible Environmental Etiological Factors in the Carcinoma of Esophagus and Stomach (Meeting Abstract).** (Eng) Memik, F. (Ataturk Univ. Faculty Medicine, Erzurum, Turkey). In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977.* International Agency for Research on Cancer. (Lyon, France): p. 66; 1977. (no refs.)

77-5940 **Esophageal Cancer Studies in the Caspian Littoral of Iran: Results of Population Studies--A Prodrone.** (Eng) Day, N. E. (World Health Organization, International Agency Res. Cancer, 150, Cours Albert-Thomas-69372, Lyon Cedex 2, France); Joint Iran-International Agency for Research on Cancer Study Group. *J Natl Cancer Inst* 59(4): 1127-1138; 1977.

Epidemiologic studies were undertaken to identify the geographic distribution of factors that might influence differences in esophageal cancer incidence along the Caspian littoral of Iran. In zones of contrasting incidence and sex ratio, information was obtained on food intake, smoking and drinking patterns (including tea), and other personal habits; occupation, economic, and agricultural practices; and methods of food storage, preservation, and preparation. The diet in the highest incidence area was markedly restricted to bread and tea. The poor quality of the diet itself was thought to have a role in the increased risk of developing esophageal cancer. The use of opium and sesame oil, consumption of sheep's milk and yogurt, the chewing of nass (confined to men), and the use of dyes (confined to women) were also more prevalent in the high-incidence areas. Typical dietary items were analyzed for polycyclic aromatic hydrocarbons, volatile nitrosamines, aflatoxins, nitrates, and nitrites. No unusual levels or geographic differences were found for any of the carcinogens tested. (42 refs.)

77-5941 **A Population-based Study of the Incidence of Bronchogenic Carcinoma (Meeting Abstract).** (Eng.) Carr, D. T. (Rochester, MN); Annegers, J. F.; Woolner, L. B.; Kurland, L. T. *Chest* 73(3): 396; 1977. (no refs.)

77-5942 **Incidence of Malignant Melanoma of the Skin in the Five Nordic Countries: Significance of**

Solar Radiation. (Eng) Magnus, K. (Cancer Registry Norway, Norwegian Radium Hosp., Oslo 3, Norway). *Int J Cancer* 20(4): 477-485; 1977.

The national cancer registries of Denmark, Norway, and Finland (covering the period 1953-1972), Iceland (1955-1974), and Sweden (1959-1971) were analyzed for trends in the incidence of malignant melanoma of the skin. More than 14,000 cases were identified and grouped by site. The incidence of malignant melanoma is similar in Denmark, Norway, and Sweden. Lower incidence rates are observed in Finland and Iceland. Time trends in incidence are remarkable and statistically significant except for Iceland, where the number of cases is very small. The period in which the incidence doubled ranges from 10 to 17 yrs. Striking sex differences are observed when the tumors are grouped according to primary site. There is a male preponderance for incidence on the neck/trunk, but the reverse is found for the lower limbs. There is only a slight increase in the incidence of malignant melanoma of the face. In contrast, there is a consistent upward trend in the incidence of tumors of the neck/trunk, particularly among men, and of the lower limbs, particularly among women. A difference between the face and the neck/trunk and lower limbs is also apparent in curves of age-specific incidence rates. The marked increase in malignant melanoma incidence in all the Nordic countries is in accordance with the hypothesis of an association between solar radiation and cutaneous melanoma. The increase may reflect changes in leisure and clothing habits. (20 refs.)

77-5943 **Alcohol, Tobacco and Age Factors in the Relative Frequency of Cancer among Males with and Without Liver Cirrhosis.** (Eng) Keller, A. Z. (Veterans Admin. Central Office, 151G, Dept. Medicine and Surgery, 810 Vermont Ave., NW, Washington, DC 20420). *Am J Epidemiol* 106(3): 194-202; 1977.

Data on white men with cancer only (Group A, 374 patients) or cancer plus liver cirrhosis (Group B, 286 patients) were analyzed to determine whether the patient groups differed significantly by age, relative frequency of cancers by site, and the daily use of tobacco and alcohol. Among the Group B patients, the liver cirrhosis was usually diagnosed 4 yr or more before squamous cell carcinoma of the mouth, pharynx, or larynx; most digestive organ cancers were diagnosed concurrently with the cirrhosis. Oral, pharyngeal, respiratory, digestive, genitourinary, and skin cancers were seen 3-4 yr earlier in Group B than in Group A. Only cancers of the mouth, pharynx, and digestive system were significantly excessive among Group B patients. Risk factors in liver cirrhosis such as the excessive use of whiskey, tobacco plus alcohol, and mixed alcoholic beverages were positively associated with cancers of the oral cavity and liver. The relative frequency of cancer of the floor of the mouth and liver was increased significantly in Group B patients who also smoked and drank heavily. When cancer patients of both groups

smoked and drank in comparable amounts, floor of the mouth and liver cancers were still significantly excessive among Group B patients. Since glycogen is stored and metabolized at both tissue sites, glucose metabolism is speculated to be a common factor in the pathogenesis of these two cancers. (13 refs.)

77-5944 **Angiosarcoma of the Liver in Great Britain, 1963-73.** (Eng) Baxter, P. J. (Health and Safety Executive, Employment Medical Advisory Service, London W2 4TF, England); Anthony, P. P.; MacSween, R. N.; Scheuer, P. J. *Br Med J* 2(6092): 919-921; 1977.

Deaths attributed to primary angiosarcoma of the liver (ASL) in Great Britain between 1963 and 1973 were reviewed by submitting available histological material to a panel of histopathologists and by obtaining full occupational and residential histories for the cases considered as ASL by the panel. An av of four cases of ASL occurred annually, but in only one-third of the cases did the panel agree with the original diagnosis. Only one of the cases was definitely linked to exposure to vinyl chloride. (17 refs.)

77-5945 **Angiosarcoma of the Liver: An Epidemiologic Survey.** (Eng) Brady, J. (Bureau Occupational Health and Chronic Disease Res., New York State Dept. Health, Empire State Plaza, Tower Building, Albany, NY 12237); Liberatore, F.; Harper, P.; Greenwald, P.; Burnett, W.; Davies, J. N.; Bishop, M.; Polan, A.; Vianna, N. *J Natl Cancer Inst* 59(5): 1383-1385; 1977.

An epidemiology survey of angiosarcoma of the liver (ASL) revealed that the annual incidence rate (cases diagnosed 1970 through 1975) among residents of New York State (excluding New York City) was 0.25 per million. A case-control study of 26 patients indicated that direct exposure to arsenic, vinyl chloride (VC), and thorium dioxide was a significantly important factor in the etiology of ASL ($p < 0.02$). Seven patients had documented exposure to these chemicals, but 19 did not. The fact that 5/19 lived nearer to VC fabrication or polymerization plants than did their matched controls indicated that indirect modes of exposure, not specifically related to occupation, might be an important factor in the etiology of ASL. The possibility that other toxic substances (chlorinated hydrocarbons) may cause ASL was also mentioned. (17 refs.)

77-5946 **Mortality among Employees of PVC Fabricators.** (Eng) Chiazzie, L. (Div. Biostatistics and Epidemiology, Dept. Community Medicine and International

Health, Georgetown Univ. Sch. Medicine, Washington, DC 20007); Nichols, W. E.; Wong, O. *J Occup Med* 19(9): 63-628; 1977.

A cross-sectional mortality study was conducted to identify lung cancer deaths among 4,341 deaths that occurred during 1964-1973 among current or former employees of 17 companies engaged in polyvinyl chloride fabrication. No lung cancer deaths were found among the study population. In addition, distributions by cause of death among white male and female employees were compared with those for the general population of the US, specific for color and sex and adjusted for age by Proportionate Mortality Ratios. Important differences in total cancer were found among white employees. They appeared to be concentrated in cancers of the digestive system, particularly cancers of the intestine. In addition, mortality from breast and urinary cancer among white female employees was high. Results suggest the need for continued investigation. (9 refs.)

77-5947 **Mortality in a Region Surrounding an Arsenic Emitting Plant.** (Eng) Pershagen, G. (Dept. Environmental Hygiene, Karolinska Inst., Stockholm, Sweden); Bolander, C. G.; Bolander, A. M. *Environ Health Perspect* 19: 13-137; 1977.

Causes of death were determined over a 14-yr period for a population near a Swedish smelter, which processes high-arsenic-content ores, and compared to a control population with a similar degree of urbanization, occupation profile, and age distribution. From 1930-1960, arsenic was emitted in the area in amounts of 1-3 tons/day, although in recent years these emissions have decreased. There were no pronounced differences in mortality rates among men and women for any causes of death other than lung cancer in men. In the exposed population, this excess was significant ($p < 0.01$) compared to lung cancer mortality in the control population. Out of 28 cases of primary respiratory cancer, 15 had been employed in the smelter. This increase was no longer significant when the occupationally exposed individuals were excluded from the mortality calculations. Therefore, the only definite conclusion that can be made is that there was a highly significant excess mortality due to primary respiratory cancer among occupationally exposed men at the smelter. (13 refs.)

77-5948 **Associations of Cancer Site and Type with Occupation and Industry from the Third National Cancer Survey Interview.** (Eng) Williams, R. R. (Dept. Internal Medicine, Cardiovascular Div., Univ. Utah Medical Center, 50 North Medical Drive, Salt Lake City, UT 84132); Hargens, N. L.; Goldsmith, J. R. *J Natl Cancer Inst* 59(4): 117-1185; 1977.

Based on 7,518 cases, associations of specific cancer

types and sites with certain occupations and industries are reported. Controls were established so that data would not reflect influences due to age, sex, race, education, use of cigarettes or alcohol, and geographic location. Extensive tables are included, and suggestions are made for further study. (12 refs.)

77-5949 **Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk.** (Eng) Occupational Safety and Health Administration (OSHA, Dept. Labor, Washington, DC 20210). *Fed Regist* 42(192): 54148-54247; 1977.

The significant provisions of three model standards proposed for occupational carcinogens by the Occupational Health and Safety Administration are summarized. The standards include an emergency temporary standard and permanent standards for toxic substances in Category I (potential carcinogens) and Category II (suggestive evidence of carcinogenicity). Each standard covers permissible exposure levels, notification of use by employers, exposure monitoring and measurements, respiratory protection, protective clothing and equipment, emergencies, housekeeping and waste disposal, hygiene facilities, medical surveillance, employee training, precautionary signs and labels, and recordkeeping. (Refs.)

77-5950 **A Death Certificate Analysis of Nasal Cancer among Furniture Workers in North Carolina.** (Eng) Brinton, L. A. (Environmental Epidemiology Branch, NCI, Bethesda, MD 20014); Blot, W. J.; Stone, B. J.; Fraumeni, J. F. *Cancer Res* 37(10): 3473-3474; 1977.

A case-control study of nasal cancer, based on death certificate statements of occupation in North Carolina counties with furniture-manufacturing industries, revealed a fourfold excess risk linked to woodworking. Of the 37 persons who died from nasal cancer in the period 1956-1974, 8 were furniture makers and 5 were sawmill workers or carpenters. Although woodworking exposures have been associated with nasal adenocarcinomas in several areas of the world, this is the first report of such a relationship in the US. (12 refs.)

77-5951 **Lung Cancer Risk Among Beauticians and Other Female Workers: Brief Communication.** (Eng) Menck, H. R. (Dept. Pathology, Univ. Southern California Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA 90033); Pike, M. C.; Henderson, B. E.; Jing, J. S. *J Natl Cancer Inst* 59(5): 1423-1425; 1977.

Lung cancer risk among occupational groups of women in

Los Angeles County for 1972-75 was analyzed. Particular attention was directed toward beauticians, for whom increased risk had already been reported. Analysis of the distribution of cancer among white female beauticians without Spanish surnames (20-64 yr of age) by anatomic site revealed a significantly ($p < 0.05$) increased risk (approx twofold) for cancer of the lung. By occupation and using the proportional incidence ratio, a statistically significant ($p < 0.05$) increased lung cancer risk was also seen for assemblers and waitresses. However, sufficient data (eg, smoking habits) for all the women were not available. (11 refs.)

- 77-5952 **Mesothelioma: Social and Occupational Aspects.** (Fre.) Gaucher, P. (28, rue du General de Sonis, 44000 Nantes, France); de Lajartre, M. *Arch Mal Prof* 38(3): 347-357; 1977.

An attempt was made to determine if 54 patients (52 men, 2 women) with pulmonary mesotheliomas, which were discovered between 1955 and 1975, had definite prior exposure to asbestos. Asbestos fibers were identified in the pleura after surgery (22 patients), thoracotomy (18), needle biopsy (6), or autopsy (8). The average age at death for 46 patients was 59.2 yr. Total excision prolonged survival by only several months. Thirty-eight of the patients were city dwellers, 16 rural inhabitants; 32 worked in shipyards, and most of the remaining patients worked in the mechanical or construction trades. Overall, 31 patients were definitely and 1 was probably exposed to asbestos. In addition, 29/31 were smokers. This inquiry confirms the relation between exposure to asbestos dust and pulmonary mesothelioma. (no refs.)

- 77-5953 **Asbestos Bodies in Lung Parenchyma in Relation to Ingestion and Inhalation of Mineral Fibers.** (Eng) Auerbach, O. (Veterans Admin. Hosp., East Orange, NJ); Hammond, E. C.; Selikoff, I. J.; Parks, V. R.; Kaslow, H. D.; Garfinkel, L. *Environ Res* 14(2): 286-304; 1977.

Lung tissues from 282 Duluth, Minnesota women who died between 1953 and 1973 were examined by light microscopy for the presence of asbestos bodies attributed to the ingestion of water contaminated with fibers from a taconite ore-processing plant in operation since 1955. The women, who had lived in Duluth for at least 15 yr, had never been occupationally exposed to asbestos particles and had not lived in neighborhoods with high levels of asbestos dust. The mean number of asbestos particles in ashed lung specimens from 96 Duluth women exposed to the contaminated drinking water for 17-18 yr was somewhat lower than the number in tissues from 96 age-matched New York City women. Moreover, the percentage of tissues with one or more asbestos bodies was not higher in this group of Duluth women than in tissues from women with no asbestos exposure or expo-

sure of 5-6 or 11-12 yr. Thus, there is no evidence that small asbestos fibers are taken into the bloodstream as a result of drinking Duluth water. In another study, more asbestos particles were found in lung specimens from 19 Patterson, New Jersey men who had lived within one-half mile of an asbestos factory than in specimens from 19 New York City men. (20 refs.)

- 77-5954 **Epidemiological Aspects of Occupational Asbestosis in the Region of Paris.** (Fre) Cabasson, C. B. (No affiliation given); Cavigneaux, A.; Delplace, Y. *Arch Mal Prof* 38(3): 373-379; 1977.

A horizontal 10-yr (1965-1975) epidemiological study in the area of Paris disclosed 52 cases (50 men, 2 women) of occupational asbestosis. Occupationally, these patients worked in contact with or in the manufacture of asbestos-containing materials. They were exposed to this risk from 14 to 27 yr. Of the 52 patients, 8 died of asbestosis, with a diagnosis of pulmonary mesothelioma in 5 and bronchopulmonary cancer in 1. All the deceased had pulmonary fibrosis. Two brief case histories of a glass blower and a painter who contracted asbestosis are also presented. (no refs.)

- 77-5955 **Cancer in Asbestos-mining and Other Areas of Quebec.** (Eng) Graham, S. (Res. Program in Social Epidemiology and Control Cancer, Dept. Sociology, State Univ. New York at Buffalo, 4224 Ridge Lea, Amherst, NY 14226); Blanchet, M.; Rohrer, T. *J Natl Cancer Inst* 59(4): 1139-1145; 1977.

The relative risks of cancer of all sites were examined in the asbestos-mining, rural, and urban regions of Quebec Province using data from the Quebec Tumor Registry for 1969-1973. The risk of pleural cancer in men in asbestos-mining regions was 8.08 times higher than that among rural residents and 2.2 times higher in adjacent counties than in other rural counties. The same relationship held for women, with the rate in asbestos-mining counties being 3.38 times that in rural counties. Urban risk was also higher than rural risk for both sexes. Cancer of the peritoneum had a risk profile similar to that of the pleura in men. Among women, no mediastinal or peritoneal cancers were noted in asbestos-mining areas, but there was a high urban risk. For lung cancer, risk in men in asbestos-mining counties was 23% higher than that in rural residents; urban rates were higher still. Women had similar rates. Cancer of the larynx had similar risks for both sexes. An increased risk of lip or salivary gland cancer was noted for men and women with increased proximity to asbestos mines. Men also had a higher risk for cancer of the tongue, mouth, small intestine, and thyroid; women were at higher risk for melanoma. There was a low risk of colon cancer in both sexes. (20 refs.)

5956 **Correlation of Cancer Death Rates with Altitude and with the Quality of Water Supply of 100 Largest Cities in the United States.** (Eng) Burton, C. (Dept. Biophysics, Health Sciences Center, Univ. West-Ontario, London, Ontario, Canada N6A 5C1); Cornhill, J. *J Toxicol Environ Health* 3(3): 465-478; 1977.

On water treatment and the quality of the finished water supply of the 100 largest US cities (population > 60 million) combined with data on cancer deaths (age-adjusted) of county or counties in which the cities lie, to look for significant correlations with altitude and with quality of water supply. The previously discovered decrease in cancer rates with increasing altitude (for countries around the world) was confirmed for these cities. Correlation coefficients, -0.46 for men and -0.32 for women, were highly significant ($p < 0.01$). The rates were then altitude-adjusted for subsequent analysis. Of the general measures of water quality, the highest correlation was with specific conductivity, total dissolved solids, and hardness; pH was not significantly correlated. Significant correlations were found for Ca^{2+} , Mg^{2+} , Na^{+} , SO_4^{2-} , and Cl^{-} concentrations, but not for F^{-} and NO_3^{-} , or nitrate concentrations, which were very low. Regression slopes for specific ions were much more uniform in terms of milliequivalents per liter than parts per million. The reduction in cancer rates appears to be nonspecific for major sites, as is the previously reported altitude effect. A possible common explanation of the altitude and water-quality correlations is discussed in terms of the acid-base balance and base reserve of the body, but there are no adequate data for the effect of increased dissolved solids in water on blood chemistry to support speculation. A regression equation combining the altitude and the specific conductivity of the water of these cities predicts the death rate from cancer to the 95% level of confidence, within $\pm 17.4\%$ for men and $\pm 17.0\%$ for women. Of the total variance in death rates, 36% is associated with these parameters combined. (13 refs.)

57 **Cancer Mortality in Relation to Asbestos in Municipal Water Supplies.** (Eng.) Wigle, D. T. (Epidemiology, L.C.D.C., Health and Welfare Canada, Tunney's Pasture, Ottawa, Ontario, K1A 0L2, Canada). *Environ Health* 32(4): 185-190; 1977.

Cancer mortality in 22 communities in Quebec grouped by degree of exposure to asbestos fibers in water supplies (high, medium high, and probable low exposures) was evaluated. Expected numbers of cancer deaths were calculated by using the Quebec age-specific (5-yr groups), sex-specific, period-specific (1965-1967, 1970-1972) mortality rates to the 1966 or 1971 census populations by age and sex for each community. The results were compared with the actual number of deaths. Excess mortality due to cancer of the stomach (men), pancreas (women), and lung (men) was observed in the two communities with known high exposure. Excess stomach and lung cancers among men may reflect

occupational exposure to asbestos. This study does not support an association between pancreatic cancer and exposure to asbestos fibers in drinking water, because there was no excess among men. A relationship between stomach cancer and waterborne asbestos likewise is not supported by these results, because of the absence of an excess cancer mortality among women. (11 refs.)

77-5958 **Some Parasites and Diseases of Estuarine Fishes in Polluted Habitats of Mississippi.** (Eng) Overstreet, R. M. (Parasitology Section, Gulf Coast Res. Lab., Ocean Springs, MS 39564); Howse, H. D. *Ann NY Acad Sci* 298: 427-462; 1977.

Parasitic and nonparasitic diseases that affect finfish and shellfish living in polluted Mississippi waters are discussed. Relationships between bacterial and viral diseases and stress caused by sublethal amounts of pollutants are noted. Tumors, including those induced by protozoans, are rarely manifest in Mississippi fish. Of those not associated with parasites, only one appears to be related to pollutants. The neoplasm, a suspected fibrosarcoma, affects $\leq 1\%$ of catches of striped mullet. It may be linked to the pollution of estuarine waters by carbon tetrachloride, chloroform, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane, and other pesticides. (95 refs.)

77-5959 **Papillomas in the Atlantic Eel (*Anguilla vulgaris*) (Meeting Abstract).** (Eng) Deys, B. F. (Lab. for Radiobiology, Plesmanlaan 121, Amsterdam, The Netherlands). In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 63; 1977. (no refs.)

77-5960 **Doubling Time and the NMR Properties of Water in Human Breast Cancer Cell Lines (Meeting Abstract).** (Eng) Beall, P. T. (Baylor Coll. Medicine, Houston, TX 77030); Cailleau, R. M.; Hazlewood, C. F. *In Vitro* 13(3): 204; 1977. (no refs.)

77-5961 **Comparative Analysis of Enterocyte Cell Population in Different Parts of the Rat Small and Large Intestines. I. Parameters of the Mitotic Cycle and Heterogeneity of the Proliferating Enterocyte Population.** (Rus.) Posharissky, K. M. (Lab. Experimental Tumors, Res. Inst. Oncology, Leningrad, USSR); Klimashevsky, V. F.; Gushchin, V. A. *Tsitologiya* 13(3): 303-317; 1977.

Enterocyte kinetics (labeling index, mitotic index, duration of mitotic cycle, proliferative pool, cell migration rate) were studied in random-bred male rats. Most proliferating cells in the small intestine were homogenous with respect to duration of the mitotic cycle (11-12 hr), but proliferating cells in the crypts of the large intestine could be subdivided into several subpopulations. In the transverse colon, 50% of the enterocytes had a mitotic cycle that lasted 11-12 hr; 18%, 18 hr; 25%, 30 hr; and 7%, 38 hr (long-cycle subpopulation). Long-cycle enterocytes comprised 27% of all the cells in the ascending colon. (26 refs.)

77-5962 Prediction of the Complete Growth Pattern of Human Multiple Myeloma from Restricted Initial Measurements. (Eng) Brunton, G. F. (Dept. Clinical Physics and Bio-Engineering, West of Scotland Health Boards, 11 W. Graham St., Glasgow G4 9LF, Scotland); Wheldon, T. E. *Cell Tissue Kinet* 10(6): 591-594; 1977.

The growth pattern of multiple myeloma was reviewed based on findings that the α and β values used to calculate growth vary in other cell lines. Contrary to what was previously believed, the two parameters were not independent but were

linearly related. Since the growth and regrowth patterns of human multiple myeloma are the same, the calculations now enable the growth pattern during therapy to be resolved into one component due to cell kill and another due to regrowth of surviving cells. It is thus possible to determine the cell kill produced by a single administration of a therapeutic agent (10 refs.)

See also:

- *(Rev.) 77-5402, 77-5403, 77-5404, 77-5407, 77-5411, 77-5413, 77-5414, 77-5417, 77-5418, 77-5419, 77-5422, 77-5423, 77-5424, 77-5426, 77-5431, 77-5440, 77-5441, 77-5442, 77-5443, 77-5444, 77-5449, 77-5454, 77-5455, 77-5457, 77-5459, 77-5460.
- *(Chem.): 77-5495, 77-5496, 77-5501, 77-5522, 77-5529, 77-5549, 77-5572, 77-5635, 77-5637, 77-5638, 77-5639.
- *(Phys.): 77-5658, 77-5667, 77-5682, 77-5683, 77-5691, 77-5692, 77-5693, 77-5694.
- *(Viral): 77-5718, 77-5719, 77-5824, 77-5825.
- *(Path.): 77-5903.

MISCELLANEOUS

7-5963 **Control of Normal Differentiation of Myeloid Leukemic Cells. XII. Isolation of Normal Myeloid Colony-forming Cells from Bone Marrow and the Sequence of Differentiation to Mature Granulocytes in Normal and D+ Myeloid Leukemic Cells.** (Eng.) Lotem, J. (Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel); Sachs, J. *J Cell Physiol* 92(1): 97-108; 1977.

An enriched population of early myeloid cells was obtained from normal mouse bone marrow by ip inoculation of mice with sodium caseinate followed 3 days later by removal of erythrocyte antibody complement (EAC) rosette-forming cells by rosette formation and Ficoll-Hypaque density centrifugation. The enriched normal myeloid progenitors without EAC rosettes were compared to D+ myeloid leukemic cells with respect to their ability to form EA and EAC rosettes, to synthesize and secrete lysozyme, and to differentiate into mature granulocytes. The enriched population had no EA or Fc (EA) rosettes and contained 87% early myeloid cells stained for myeloperoxidase and/or AS-D-chloroacetate esterase, 7% cells in later stages (ring forms) of myeloid differentiation, and 6% unstained cells, 2% of which were small lymphocytes. The normal early myeloid cells were induced to differentiate by the macrophage and granulocyte inducer (MGI) in mass culture in liquid medium to mature granulocytes and macrophages. The sequence of granulocyte differentiation was the formation of EA and EAC rosettes, followed by the synthesis and secretion of lysozyme and morphological differentiation to mature cells. D+ myeloid leukemic cells with no EA or EAC rosettes had a similar morphology to normal early myeloid cells and showed the same differentiation sequence. The induction of EA and EAC rosettes occurred at the same time in both the normal and D+ leukemic cells, but lysozyme synthesis and the formation of mature granulocytes were induced later in the leukemic cells than in the normal ones. This system for enrichment of early myeloid colony-forming cells and induction of differentiation in these populations should be useful in studying the mode of action of compounds that can induce some of the differentiation stages in D+ leukemic cells and in studying whether disorders in granulopoiesis are caused directly by changes in the early myeloid cells or indirectly by another mechanism. (42 refs.)

7-5964 **Regulation of CFU-S Proliferation by Locally Produced Endogenous Factors.** (Eng) Wright, G. (Paterson Labs., Christie Hosp., Manchester M20 9BX, England); Lord, B. I. *Biomedicine [Express]* 27(6): 215-218; 1977.

The role of local factors in the differential proliferation of colony-forming stem cells (CFU-S's) in bone marrow and effects of phenylhydrazine (PHZ)-treated BDF₁ mice was

investigated. Seven days after the first of three PHZ injections (60 mg/kg, sc), the bone marrow CFU-S level was 50% of the control level, and 40% of the CFU-S's were in DNA synthesis. When bone marrow cells from PHZ-treated mice were incubated for 2 hr with irradiated spleen cells from the same animals, the proportion of marrow CFU-S's in DNA synthesis declined to < 10%. Conversely, the addition of irradiated bone marrow cells to spleen cultures rapidly increased the percentage of spleen CFU-S's in DNA synthesis. The results suggest that local stimulatory and inhibitory factors act against each other, directly or indirectly, to control CFU-S proliferation rates. (13 refs.)

77-5965 **Testing the Commitment Theory of Cellular Aging.** (Eng) Holliday, R. (Genetics Div., Natl. Inst. Medical Res., Mill Hill, London NW7 1AA, England); Huschtscha, L. I.; Tarrant, G. M.; Kirkwood, T. B. *Science* 198(4315): 366-372; 1977.

The commitment theory may explain both the finite life span of diploid fibroblasts and the apparent immortality of transformed lines. On division, potentially immortal cells are assumed to generate with some fixed probability cells committed to senesce after a specific number of divisions. During the period between commitment and senescence, the cells are assumed to maintain normal growth, so that the uncommitted cells are diluted by committed ones and may ultimately be lost in subculturing. Several predictions of this model are described, and experiments strongly supporting the theory are reported. It is concluded that the limited growth of diploid fibroblasts is an artifact of normal culturing procedures. (27 refs.)

77-5966 **Regulation of Requirements for the Anchorage-independent Growth of Syrian Hamster Fibroblasts by Somatic Mutation.** (Eng.) Leavitt, J. C. (Dept. Biochemical and Biophysical Sciences, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD 21205); Crawford, B. D.; Barrett, J. C.; Ts'o, P. O. *Nature* 269(5623): 63-65; 1977.

The ability of cells of the highly tumorigenic Syrian hamster fibroblast line, BP6T, to form colonies when suspended in semisolid agar was investigated. The results indicate that the colony-forming ability of these cells depended on their use of exogenous purines via the hypoxanthine phosphoribosyltransferase (HPRT)- and adenine phosphoribosyltransferase (APRT)-mediated pathways. Furthermore, this anchorage-independent property can be inhibited by a somatic mutation at the HPRT locus. Other in vitro properties, such as cloning

efficiency in liquid medium and enhanced fibrinolytic activity, were essentially unaltered by the forward mutation of the HPRT locus. Population-doubling times and cell-saturation densities were also unchanged. In conclusion, although somatic mutations can lead to altered anchorage requirements in this cell line, the tumorigenic potential of these cells need not be lost. Therefore, alterations in requirements for anchorage-independent growth in vitro may not necessarily correlate with malignancy. (15 refs.)

- 77-5967 Regulation of Cell Division and Malignant Transformation: A New Model for Control by Uptake of Nutrients.** (Eng) Bhargava, P. M. (Div. Biochemistry, Regional Res. Lab., Hyderabad 500 009, India). *J Theor Biol* 68(1): 101-137; 1977.

A comprehensive model of the regulation of normal growth and malignant transformation is presented. The model postulates four chemical (*I*, Anti-*I*, SF1, and SF2) and two structural (Sites A and Sites B) entities. Sites A and B are functionally different transport sites on the membrane for essential nutrients. Sites A are open in resting cells and need a serum factor, SF1, for operation at V max. Sites B are closed in resting cells but open in dividing cells; the "on-off" control of Sites B is achieved through *I*, a protein with a high rate of turnover and two binding sites. Sites B are closed when *I* is bound to them; the affinity of *I* for Sites B increases when one molecule of *I* links two Sites B. A second serum factor (SF2), Anti-*I* when released from the cells (eg, as a result of tissue damage), and other external triggers for cell division (such as mitogenic hormones) destroy or inactivate *I*, or prevent its binding to Sites B. The opening of Sites B enhances the rate of nutrient uptake; the resulting increase in the intracellular concentration of one or more of the nutrients starts the programmed operation of events that culminate in cell division. Two possible mechanisms for the initiation of this program are suggested. Growth ceases as a consequence of reestablishment of the *I* function on the membrane. Malignant transformation is defined as an inheritable intracellular event, spontaneous or induced, that interferes with the production or activity of *I* and leads to a loss of the capacity for transition from the dividing to the resting state. Likely candidates for the various entities proposed are listed. (430 refs.)

- 77-5968 Cell Cycle Regulation by Growth Factors and Nutrients in Normal and Transformed 3T3 Cells** (Meeting Abstract). (Eng) Paul, D. (Salk Inst., San Diego, CA 92112). *In Vitro* 13(3): 141; 1977. (no refs.)

- 77-5969 Biological and Biochemical Characterization of Normal and Transformed BALB/c Fibroblasts**

(Meeting Abstract). (Eng.) Van Nest, G. A. (Univ. Arizona, Tucson, AZ 85721). *Diss Abstr Int [B]* 38(3): 1196; 1977. (no refs.)

- 77-5970 Matrix-perfusion Cultivation of Human Choriocarcinoma and Colon Adenocarcinoma Cells** (Meeting Abstract). (Eng) Rutzky, L. P. (Northwestern Univ. Med. Sch., Chicago, IL 60611); Tomita, J. T.; Calenoff, M. A.; Kahan, B. D. *In Vitro* 13(3): 191; 1977. (no refs.)

- 77-5971 Influence of Serum on the Growth of Human Breast Carcinoma Cells In Vitro** (Meeting Abstract). (Eng) Lasfargues, E. Y. (Institute for Medical Res., Camden, NJ 08103); Coutinho, W. G. *In Vitro* 13(3): 204; 1977. (no refs.)

- 77-5972 Differential Serum Requirement for Attachment by Normal and Transformed Cells In Vitro** (Meeting Abstract). (Eng) Rajaraman, R. (Dept. Medicine, Faculty Medicine, Dalhousie Univ., Halifax, N. S., Canada); MacSween, J. M.; Fox, R. A. *In Vitro* 13(3): 205; 1977. (no refs.)

- 77-5973 Effect of Cytochalasin B on Normal and Transformed Cultured Cells: Correlation Between Nucleation and Survival** (Meeting Abstract). (Eng) Putzrath, R. K. (Temple Univ., Philadelphia, PA 19122); Brownstein, B. L. *In Vitro* 13(3): 166; 1977. (1 ref.)

- 77-5974 The Effect of Pentadecan-2-one on HeLa Cell-Agar Debonding** (Meeting Abstract). (Eng) Fletcher, R. D. (Univ. Pittsburgh, Pittsburgh, PA 15261); Breitling, S. M.; Naccarato, W. F.; Gilbertson, J. R.; Adamiak, J. K.; Williams, M. L. *In Vitro* 13(3): 154; 1977. (no refs.)

- 77-5975 Culture of Mouse Preputial Sebocyte Tumor Cells** (Meeting Abstract). (Eng) Rossman, T. (N.Y.U. Medical Center, New York, NY 10016); Stone, D.; Prutkin, L.; Wheatley, V.; Troll, W. *In Vitro* 13(3): 165-166; 1977. (no refs.)

5976 Polyamine-stimulated Growth of Cultured Rat Urinary Bladder Epithelial Cells. (Eng.) Ros-
J. A. (Veterans Admin. Hosp., 1030 Jefferson Ave.,
Memphis, TN 38104); Douglas, C. J.; Irving, C. C. *Cancer*
37(1): 239-243; 1977.

method for isolating and culturing rat bladder epithelial
cells to obtain long-term growth potential was developed by
adding putrescine, spermine, and spermidine to the culture
medium. Cells grew for 12 wk without subculturing and sub-
cultures carried through five passages. (21 refs.)

5977 Induction, Suppression, and Etiology of Precan-
cerous Changes in Organ-cultured Urinary
Bladder Epithelium (Meeting Abstract). (Eng.) Reese, D. H.
Cancer Branch, NCI, NIH, Bethesda, MD 20014);
Edman, R. D. *In Vitro* 13(3): 178; 1977. (no refs.)

5978 Cell Surface Changes Associated with Malignant Transformation of Bladder Epithelium In
Vivo. (Eng.) Kahan, B. D. (Div. Immunology, Dept. Bio-
chemistry, Univ. Texas Medical Sch. at Houston, Houston,
TX 77030); Rutzy, L. P.; Kahan, A. V.; Oyasu, R.; Wise-
man, F.; LeGrue, S. *Cancer Res* 37(8, part 2): 2866-2871;
1977.

Cell surface properties of two in vitro-induced bladder tu-
mor cell lines were compared with those of normal ACI/
Sprague-Dawley rat epithelium. The tumor lines were H-3, induced
by N-butyl-N-(4-hydroxybutyl)nitrosamine and urea, and H-4,
induced by N-butyl-N-(3-carboxypropyl)nitrosamine and
urea. Under scanning electron microscopy, the normal uro-
thelial cell surfaces were devoid of microvillous structures
and displayed only a few signs of budding. The tumor cells,
however, had a rich, pleomorphic microvillous system that
was densely distributed over mounds. The microvilli were
irregular, disorganized structures with a variable density of
distribution. There were also pleomorphic, spherical surface
protrusions, occasionally joined to the cell by narrow con-
nections. The molecular wt profiles of proteins dispersed
in purified plasma membrane fractions showed significant
differences: normal cells had a greater content of 45,000
(K), 66K, and 200K proteins compared with H-3 and H-4
cells, but the latter had more 50K, 56K, and 98K proteins.
These differences might actually reflect qualitative changes,
since the analysis discriminates only all proteins of a given
molecular wt. Two-dimensional electrophoretic analysis of 3
KCl extracts revealed 23 iodinated proteins in the ex-
tracts of normal urothelium, 17 in H-3, and 18 in H-4. The
pleomorphic surface microvilli, distinctive membrane com-
ponents, and unique proteins may represent focal points for
design of new diagnostic and therapeutic tools. (14 refs.)

77-5979 The Role of Plasma Membrane and Intracellu-
lar Microskeletal Elements in Determining the
Lectin Agglutinability of Two CHO Sub-clones. (Eng.) Noo-
nan, K. D. (Dept. Biochemistry and Molecular Biology, J.
Hillis Miller Health Center, Univ. Florida, Gainesville, FL
32610); van Veen, J.; Roberts, R. M. *Prog Clin Biol Res* 17:
521-530; 1977.

Lectin-initiated cell agglutination was investigated using the
K-1 line and the H-7 clone of Chinese hamster ovary cells.
Reduced lectin agglutinability was dependent on a protease-
labile structure and the maintenance of the cellular mi-
crotubules and microfilaments in a polymerized state. Ag-
glutination with concanavalin A demonstrated a correlation
between enhancement of lectin receptor site clustering and
agglutination. However, the H-7 cell line could be modified
so that the surface assumed the structure of lectin-initiated
agglutination without any long range clustering of receptors.
(15 refs.)

77-5980 Membrane Glycoprotein Changes in Primary
Mammary Tumors Associated with Autono-
mous Growth. (Eng.) Smets, L. A. (Div. Cell Biology, Neth-
erlands Cancer Inst., Antoni van Leeuwenhoek Lab., 108
Sarphatistraat, Amsterdam, Netherlands); Van Beek, W. P.;
Van Nie, R. *Cancer Lett* 3(3-4): 133-138; 1977.

An investigation was made to determine whether membrane
glycoprotein alterations are associated with in vivo neoplastic
growth. Hormone-dependent and spontaneous hormone-
independent mammary tumors and uninvolved control
glands of the GR mouse were explanted in tissue culture and
grown in the presence of radioactive fucose. Chromatogra-
phy of differentially labeled glycopeptides isolated from the
cell-surface membranes revealed that the glycopeptides from
the malignant cells were generally larger. This increased size
was attributed to the presence of more complex, branched
carbohydrate structures enriched in terminal sialic acid resi-
dues. However, this difference was noted only when the cells
were cultured from hormone-independent tumors, and not
from hormone-dependent tumors. Thus, there is a correlation
between biochemical changes and a biological property of
neoplastic cells in vivo: the acquisition of autonomous, hor-
mone-independent growth by murine adenocarcinoma cells.
(10 refs.)

77-5981 Comparison of Cell-Surface Glycoproteins of
Rat Hepatomas and Embryonic Rat Liver.
(Eng.) Van Beek, W. P. (Div. Cell Biology, Antoni Van Leeu-
wenhoek-Huis, Netherlands Cancer Inst., Amsterdam, Ne-
therlands); Emmelot, P.; Homburg, C. *Br J Cancer* 36(2):
157-165; 1977.

A comparison was made of the cell-surface glycoprotein of three rat hepatoma strains (Novikoff N₁S₁-67, ST-1, and Reuber H-35) and late embryonic liver. Elution profiles from gel filtration techniques yielded more high mol wt glycopeptides for the hepatomas than for normal liver. Three factors were identified that may augment the fraction of early-eluting tumor glycopeptides: an increase of neuraminidase-sensitive sialic acid; an increase of neuraminidase-insensitive sialic acid that was sensitive to mild HCl hydrolysis; and the presence of sugar sulfate groups contributing to a restricted extent, relative to a possible unknown factor(s). The increase in glycopeptides appears to be a marker of tumorigenicity, ie, a biochemical parameter distinguishing normal from cancerous cells. (41 refs.)

- 77-5982 α_1 -Acid Glycoprotein and α_1 -Antitrypsin as Mitotic Inhibitors in Regenerating Rat Liver. (Eng.) Onda, H. (First Dept. Internal Medicine, Faculty Medicine, Univ. Tokyo, Hongo 7-3-1, Bunkyo-Ku, Tokyo 113, Japan). *Gann* 68(3): 301-306; 1977.

The time course changes in the intravascular concentration of plasma proteins, especially α_1 -acid glycoprotein, after partial hepatectomy were investigated in 40 male Wistar rats. The mitotic index began to increase between 18 and 24 hr after partial hepatectomy. It rapidly reached a peak at 27.5 hr, but by 168 hr, it had returned to near the control level. The total plasma protein concentration in the partially hepatectomized rat fell slowly, reaching a minimum at 24 hr and then rising to the preoperative control value at 168 hr. Changes in the concentration of α_2 -, β -, and γ -globulins were similar to that of total protein. The concentration of α_1 -globulin, however, decreased sharply to approx one-third that of nonoperated rats at 18 hr after partial hepatectomy; thereafter, it rose to its highest value at 168 hr. The α_1 -acid glycoprotein level rose steadily to its highest value of about four times the control level at 27.5 hr and thereafter fell slowly. The α_1 -antitrypsin level decreased sharply to about one-sixth of the control level by 18 hr after partial hepatectomy and thereafter rose to its highest value at 168 hr. These results indicate that α_1 -acid glycoprotein is excreted from the hepatocytes in the residual liver early after partial hepatectomy, before mitosis, and that there is a relationship between intravascular concentration of α_1 -antitrypsin and the number of protein-producing hepatocytes in the residual liver, suggesting a close correlation of this protein to the occurrence and suppression of mitosis. (27 refs.)

- 77-5983 Cells Derived from a Mammary Carcinoma Produce Type IV Collagen In Vitro (Meeting Abstract). (Eng.) Daniel, J. C. (Northwestern Univ. Medical Sch., Chicago, IL 60611); Kuettner, K. E. *In Vitro* 13(3): 204; 1977. (no refs.)

- 77-5984 Rat Embryo Nonhistone Chromosomal Proteins: Interaction In Vitro with Normal and Bromodeoxyuridine-substituted DNA. (Eng) Schwartz, S. A. (Dept. Pathology, Univ. Chicago, Chicago, IL 60637). *Biochemistry* 16(18): 4101-4108; 1977.

The molecular nature of rat embryo cell nonhistone chromosomal proteins (NHCP) was examined, and their interaction with normal and 5-bromodeoxyuridine (BUdR) substituted rat DNA in vitro was determined. Following extraction, purification, and iodination with ¹²⁵I, the proteins were characterized by amino acid analysis and polyacrylamide gel electrophoresis and reconstituted with DNA in vitro by affinity chromatography and gradient dialysis recombination. A subfraction of rat embryo NHCP demonstrated an ability to bind in vitro to homologous and, to a slight extent, heterologous DNA. Nearly 20% of the NHCP mass was able to bind to DNA from any rat tissue source. The qualitative characterizations of DNA-binding NHCP were consistently similar, regardless of whether the recombinations took place on DNA absorbed to cellulose or in solution during stepwise dialysis. Although similar types and amounts of rat embryo NHCP bound to BUdR-treated as well as to untreated rat DNA in vitro, the strength of the binding was consistently and significantly greater with bromouracil-substituted DNA. The mol wts ranged from 10,000 to 140,000 for total rat embryo NHCP, but the predominant DNA-binding subfractions consisted of lower mol wt species. These findings support the hypothesis that the presence of bromouracil in DNA with an overall increased potential for NHCP binding may result in a cellular inability to regulate certain genetic functions. This mechanism may account for BUdR-mediated effects at the transcriptional level. (35 refs.)

- 77-5985 Bromodeoxyuridine (BUdR) Treatment of Melanoma Cells Decreases Cellular Proteolytic Activity. (Eng.) Evans, I. (Dept. Pharmacology and Toxicology, Univ. Rochester Cancer Center, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY 14642); Bosmann, H. B. *Exp Cell Res* 108(1): 151-155; 1977.

A substantial decrease in tumorigenicity and melanization occurred when B16 melanoma cells were cultivated in 10 μ g/ml bromodeoxyuridine (BUdR) for 1-2 days. Both parameters continued to decline with longer BUdR incubation, but this decline was reversible. Plasminogen activator protease activity, acid polysaccharide metabolism, and the size of various amino acid pools were also affected. (30 refs.)

- 77-5986 Compartmentalization of Tyrosine for Melanin Synthesis in Hamster Melanoma Cell Line RPMI-3460 (Meeting Abstract). (Eng) Farishian, R. A. (Wi-

ar Inst., Philadelphia, PA 19104); Whittaker, J. R. *In Vitro* 13(3): 149; 1977. (no refs.)

-5987 **Temporal Relationships Between DNA Synthesis and Growth Inhibition in Dexamethasone-treated Rat Glioma Monolayer Cultures (Meeting Abstract).** (Eng) Grasso, R. J. (Coll. Med., Univ. So. Fla., Tampa, FL 33612); Wodzinski, S. F.; Johnson, C. E. *In Vitro* 13(3): 190; 1977. (no refs.)

-5988 **Establishment of Mouse Embryo Cells In Vitro: Relationship of DNA Synthesis, Senescence, and Malignant Transformation (Meeting Abstract).** (Eng) Creek, R. L. (Univ. California, Santa Cruz, CA 95064); Bowman, P. D.; Daniel, C. W. *In Vitro* 13(3): 185-186; 1977. (no refs.)

-5989 **Distribution of MOPC-315 Light Chain Messenger RNA in Free and Membrane-bound Polyribosomes.** (Eng.) Okuyama, A. (Roche Inst. Molecular Biology, Nutley, NJ 07110); McInnes, J.; Green, M.; Pestka, J. *Biochem Biophys Res Commun* 77(1): 347-351; 1977.

molecular hybridization with purified, ³H-labeled, complementary DNA (cDNA) was used to quantitate the distribution of immunoglobulin light-chain messenger RNA (L³¹⁵ RNA) of the mouse MOPC-315 plasmacytoma. Polyadenylated mRNA fractions were isolated by oligo(dT)-cellulose chromatography from membrane-bound polyribosomes, free polysomes, and 100,000 x g supernatant fractions (100) from 20 g of MOPC-315 plasmacytoma. The mRNA obtained (110, 140, and 17 µg, respectively) was annealed with approx 500 cpm³H-cDNA at 68 C in 0.4 M sodium phosphate, pH 7.0, for 60 hr. Membrane-bound polysomal RNA contained 2.7 and 3.7 times more L³¹⁵mRNA per microgram of mRNA than the other two fractions. Free polysomes contained about one-third of the total light-chain RNA present in MOPC-315 plasmacytoma. Thus, immunoglobulin mRNA is not found exclusively on membrane-bound polyribosomes. (13 refs.)

-5990 **Two Enzymes Are Required for Strand Incision in Repair of Alkylated DNA.** (Eng) Laval, J. (Laboratoire Associé n 147, CNRS et Unité 147 INSERM, Institut Gustave-Roussy, 94800 Villejuif, France). *Nature* 269(5631): 829-832; 1977.

The incision of alkylated DNA was studied using a DNA N-glycosidase that excises 3-methyladenine and an endonu-

lease that acts on apurinic sites. In PM2-DNA incubated with methyl methanesulfonate, the av number of nicks per molecule (0.15) was not significantly altered by the addition of DNA N-glycosidase (0.17 nicks) or endonuclease (0.16 nicks) alone. In contrast, sequential incubation with the two enzymes resulted in an av of 1.05 nicks per molecule. The results are evidence of a two-step mechanism for the incision of alkylated DNA. (32 refs.)

77-5991 **Ornithine Decarboxylase and Polyamines in Liver and Kidneys of Rats on Cyclical Regimen of Protein-free and Protein-containing Diets: Relationship to Deoxyribonucleic Acid Synthesis in Liver.** (Eng) Farwell, D. C. (Dept. Biochemistry, Univ. New Hampshire, Durham, NH 03824); Miguez, J. B.; Herbst, E. J. *Biochem J* 168(1): 49-56; 1977.

The activity of ornithine decarboxylase (OD) in the liver and kidneys of male Sprague-Dawley rats maintained on a cyclical regimen of protein-free and protein-containing diets was investigated. Enzyme activity was elevated on each day of a 3-day period of refeeding of protein after a 3-day protein-free diet. The activation of OD in the liver and kidneys of rats refed protein was demonstrable throughout 16 cycles of alternating 3-day periods of protein-free and protein-containing diets. The magnitude of the stimulation of kidneys diminished from twentyfold in the first cycle to fivefold (compared with animals fed with protein-free diet) in the later cycles of protein-refeeding. The stimulation of enzyme activity in the liver decreased from twentyfold in the first cycle to approx tenfold in later cycles. The spermidine concentration in the liver increased by approx 50% during cycling from protein-free to protein-containing diets. Spermine was unchanged, and putrescine was maintained at a low concentration (approx one-fifth to one-tenth that of spermidine) after protein refeeding. The incorporation of [³H]thymidine into liver DNA increased tenfold in animals refed with protein compared with animals receiving protein-free diets. The activation of OD by refeeding or protein was inhibited 90% by the injection of propane-1,3-diamine during refeeding. Stimulation of DNA synthesis was inhibited 60% by multiple injections of propane-1,3-diamine during protein refeeding. (27 refs.)

77-5992 **An Adenylate Cyclase of Brain Reflects Propensity for Breast Cancer in Mice.** (Eng.) Cotzias, G. C. (Dept. Neurology, New York Hosp.-Cornell Medical Center, New York, NY 10021); Tang, L. C. *Science* 197(4308): 1094-1096; 1977.

A high propensity for breast cancer in female C57B1/6J mice was associated with low dopamine-stimulated adenylate cyclase activity in the brain and low motor responses to injections of levo-3,4-dihydroxyphenylalanine (L-dopa, 1.2 mg/g,

ip). The mean activity of the cerebral cyclase in tumor-bearing animals that received L-dopa (40 mg/g chow x 3 mo) was 53 picomoles (pmol) of cyclic AMP, whereas that of tumor-free mice was 108.7 pmol ($p < 0.5$). These results strongly suggest that the behavioral function of the cyclase is linked to its ability to predict propensity for breast cancer. (17 refs.)

- 77-5993 **Guanylate Cyclase in Human Brain Tumors: Regulation of Cellular Growth.** (Eng.) Kura, K. (Dept. Pharmacology and Pharmacognosy, Univ. Milan, 20129 Milan, Italy); Frattola, L.; Spano, P. F.; Trabucchi, M. *Pharmacol Res Commun* 9(6): 579-586; 1977.

In view of the hypothesis that cyclic guanosine-3',5'-monophosphate (cGMP) may be a regulator of cell proliferation and development, intracellular guanylate cyclase activity was determined in normal human brain and brain tumors. Guanylate cyclase activity (expressed as picomoles of cGMP/min/mg protein) was found to be 75.5 in normal cortex grey matter and 72.9 in normal cortex white matter. This activity appeared depressed in glioblastoma (28.2) and in neurinoma (22.1). However, an increased activity was found in meningioma (247.2) and in oligodendroglioma (111). The apparent K_m was 0.11 mM for the soluble enzyme from either normal cortex or tumors, although some difference in V_{max} was noted. In the particulate fraction of the enzyme, however, the apparent K_m for GTP was lower in the tumors (0.09 mM) than in the normal cortex (0.29 mM). (19 refs.)

- 77-5994 **A Serum Factor that Increases Alkaline Phosphatase Specific Activity in HeLa (Meeting Abstract).** (Eng) Carlson, C. W. (Alfred I. duPont Inst., Wilmington, DE 19899). *In Vitro* 13(3): 162; 1977. (no refs.)

- 77-5995 **Hormonal Requirements for Growth In Vitro of Pregnancy-dependent Mouse Mammary Tumors (Meeting Abstract).** (Eng) Harbell, J. W. (Univ. California, Santa Cruz, CA 95064); Papkoff, J. S.; Daniel, C. W. *In Vitro* 13(3): 203-204; 1977. (no refs.)

- 77-5996 **Effect of Hormones on the Survival of Mammary Tumours In Vitro (Meeting Abstract).** (Eng) Kesava Rao, K. V. (Biology Division, Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay 400 012 India);

Pai, S. R.; Bhat, A. V.; Bapat, C. V. *In Vitro* 13(3): 205; 1977. (no refs.)

- 77-5997 **Catecholamine Hormone Receptors Are Reduced on Chronic Lymphocytic Leukaemia Lymphocytes.** (Eng) Sheppard, J. R. (Dight Inst. Human Genetics, Dept. Genetics and Cell Biology, Univ. Minnesota Medical Sch., Minneapolis, MN 55455); Gormus, R.; Mowdow, C. F. *Nature* 269(5630): 693-694; 1977.

A study of adenylate cyclase activity in lymphocytes from patients with chronic lymphocytic leukemia (CLL) showed that the enzyme was unresponsive to the β -adrenergic agonist isoprenaline. However, the enzyme was stimulated by flunarizine, which indicated that its catalytic component was functioning normally. The density of β -adrenergic hormone receptor sites, measured by dihydroalprenolol binding, was decreased in the CLL lymphocytes. This alteration in catecholamine receptor sites may explain the depressed cyclic AMP levels in CLL lymphocytes. (28 refs.)

- 77-5998 **Fluidity of Membrane Lipids in Human Lymphoblastoid Cell Lines (Meeting Abstract).** (Eng) Petitou, M. (Dept. Cancerologie et d'Immunogenetique, Villejuif, France); Tuy, F.; Rosenfeld, C.; Inbar, M. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 34; 1977. (no refs.)

- 77-5999 **Comparative Investigation of Lipid Classes and Fatty Acids in Crude Membrane Fractions of Normal and Malignant GR Mouse Mammary Tissue (Meeting Abstract).** (Eng) Nannestad-Hansen, F. (Fibiger Lab., Copenhagen, Denmark). In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 34; 1977. (no refs.)

- 77-6000 **Plasmids of *Agrobacterium Tumefaciens* and Their Role in Crown Gall Tumorigenesis (Meeting Abstract).** (Eng) Sciaky, D. (Washington State Univ., Pullman, WA 99163). *Diss Abstr Int B* 38(3): 1050; 1977. (no refs.)

Author Index

- Aaronson, S. A., 77-5772, 77-5778
 Ablashi, D. V., 77-5934
 Abramson, R. K., 77-5592
 Adamiak, J. K., 77-5974
 Adelusi, B., 77-5927
 Adolphs, H. D., 77-5464
 Advani, S. H., 77-5900
 Agarwal, S. S., 77-5634
 Ahmed, M., 77-5775, 77-5777
 Ahokas, J. T., 77-5553
 Akino, T., 77-5481
 Alderson, T., 77-5651
 Allen, J. R., 77-5505
 Allison, C., 77-5718
 Althoff, J., 77-5605, 77-5607
 Alwine, J. C., 77-5786
 Amchenkova, A. M., 77-5698
 Amin, M., 77-5829
 Andersen, P. R., 77-5771
 Anderson, C., 77-5835
 Anderson, C. W., 77-5830
 Andrese, A. P., 77-5822
 Angel Navarro, M., 77-5579
 Annegers, J. F., 77-5941
 Anthony, P. P., 77-5944
 Appella, E., 77-5885
 Archer, M. C., 77-5604
 Argyris, T. S., 77-5587
 Arrendale, R. F., 77-5596
 Asano, S., 77-5858
 Asquith, J. C., 77-5652
 Astier, T., 77-5719, 77-5735
 Astill, B. D., 77-5610
 Atherton, D. R., 77-5662
 Atkins, N. B., 77-5907
 Atkins, J. F., 77-5830
 Auerbach, O., 77-5953
 Aupoix, M., 77-5710, 77-5711
 Autrup, H., 77-5568, 77-5570, 77-5603
 Avertsev, S. A., 77-5482
 Babusikova, O., 77-5739
 Bacchetti, S., 77-5815
 Badea, E., 77-5854, 77-5855
 Bader, J. P., 77-5702
 Baines, P., 77-5617
 Bajerska, A., 77-5650
 Baker, D. G., 77-5586
 Baker, M. C., 77-5907
 Baker, S., 77-5580
 Balaban-Malenbaum, G., 77-5902
 Baldwin, R. W., 77-5427
 Baluda, M. A., 77-5703
 Bannasch, P., 77-5614
 Bapat, C. V., 77-5996
 Bar, T., 77-5844
 Bara, A., 77-5513
 Barbacid, M., 77-5772, 77-5778
 Barbanti-Brodano, G., 77-5843
 Barbin, A., 77-5616
 Bardawil, W. A., 77-5904
 Barker, S. T., 77-5781
 Baron, D., 77-5640
 Barrett, J. C., 77-5556, 77-5966
 Barrett, L. A., 77-5570
 Basilico, C., 77-5760
 Basombrio, M. A., 77-5864, 77-5866
 Baumgartener, L. E., 77-5722
 Baxter, C. S., 77-5536
 Baxter, P. J., 77-5944
 Bazlova, L. S., 77-5500
 Beall, P. T., 77-5960
 Beard, J., 77-5856
 Beaumont, L., 77-5853
 Becchetti, A., 77-5629
 Beckman, G., 77-5639
 Beckman, L., 77-5639
 Beebe, G. W., 77-5694
 Bellett, A. J., 77-5836
 Bendich, A., 77-5919
 Bendinelli, M., 77-5732
 Bentvelzen, P., 77-5849
 Benveniste, R. E., 77-5780
 Benz, E. W., 77-5763
 Berg, P., 77-5799, 77-5800
 Berg, T., 77-5922
 Berget, S. M., 77-5834
 Berggren, K. E., 77-5507
 Bergholz, C., 77-5779
 Berky, J. J., 77-5753
 Bern, H. A., 77-5524
 Berry, D. L., 77-5538, 77-5548
 Besser, G. M., 77-5530
 Beth, E., 77-5807
 Beug, H., 77-5779
 Bhargava, P. M., 77-5967
 Bhat, A. V., 77-5996
 Bhisey, A. N., 77-5900
 Bhisey, R. A., 77-5585
 Biaglow, J. E., 77-5625
 Biasi, G., 77-5745
 Bignon, J., 77-5647
 Bills, D. D., 77-5506
 Birkenmeier, E. H., 77-5787
 Bischoff, P., 77-5863
 Bishop, M., 77-5945
 Black, H. S., 77-5421
 Black, V. L., 77-5535
 Blanchet, M., 77-5955
 Blankstein, L. A., 77-5730
 Blattner, W. A., 77-5441
 Blendis, L., 77-5476
 Block, N. L., 77-5915
 Bloomfield, C. D., 77-5897
 Blot, W. J., 77-5931, 77-5932, 77-5950
 Blum, S. C., 77-5558
 Bobrova, T. S., 77-5851
 Bodell, W. J., 77-5626
 Bohuon, C., 77-5918
 Bolande, R. P., 77-5445
 Bolander, A. M., 77-5947
 Bollinger, D. M., 77-5567
 Bologna, L., 77-5854
 Boman, D., 77-5922
 Bombi, J. A., 77-5921
 Borden, E. C., 77-5842
 Bordes, R., 77-5579
 Borenfreund, E., 77-5919
 Borgatti, M., 77-5843
 Bortoloni, W., 77-5843
 Bosmann, H. B., 77-5985
 Bots, G. T., 77-5901
 Bowen, J. M., 77-5852
 Bowers, T. K., 77-5897
 Bowie, M., 77-5577
 Bowman, P. D., 77-5988
 Boyar, R. M., 77-5577
 Bracken, W. M., 77-5544
 Brackmann, K. H., 77-5832
 Brady, J., 77-5945
 Brankow, D. W., 77-5539
 Brash, D., 77-5411
 Braun, A., 77-5677
 Braun, R., 77-5812
 Brauner, J. A., 77-5873
 Bredberg, A., 77-5668
 Breitling, S. M., 77-5974
 Brezina, P., 77-5923
 Bridges, J. W., 77-5533, 77-5563
 Brimer, P. A., 77-5680, 77-5681
 Brinton, L. A., 77-5950
 Brison, O., 77-5840
 Brocheriou, C., 77-5666
 Bromely, P. A., 77-5700
 Brookes, P., 77-5584
 Brouty-Boye, D., 77-5684
 Brown, R. A., 77-5549
 Brown, R. L., 77-5726
 Brownstein, B. L., 77-5973
 Bruenger, F. W., 77-5662
 Bruggeman, W. A., 77-5484
 Bruguera, M., 77-5921
 Brunton, G. F., 77-5962
 Buchman, T. G., 77-5817
 Budinger, J. M., 77-5577
 Budmen, M. B., 77-5872
 Budunova, I. V., 77-5559
 Burlington, H., 77-5655, 77-5655
 Burnett, W., 77-5945
 Burse, V. W., 77-5486
 Burton, A. C., 77-5956
 Busbee, D. L., 77-5591
 Buster, D. S., 77-5662
 Buty, S. G., 77-5544
 Byers, V. S., 77-5882
 Byrnes, J. J., 77-5535
 Cabanne, F., 77-5937
 Cabasson, C. B., 77-5954
 Cabral, G. A., 77-5608
 Cabral, J. R., 77-5483
 Cailleau, R., 77-5908
 Cailleau, R. M., 77-5960
 Cajean, C., 77-5791
 Calafat, J., 77-5720
 Calenoff, M. A., 77-5970
 Callen, D. F., 77-5511
 Calvert, J. P., 77-5598
 Camacho, L., 77-5921
 Campadelli-Fiume, G., 77-5813
 Campbell, F. R., 77-5895

- Campbell, J., 77-5938
 Campbell, R. L., 77-5474
 Canti, G., 77-5530
 Cantoni, G. L., 77-5702
 Cantrell, E. T., 77-5591
 Capparell, N. J., 77-5618
 Carley, W. W., 77-5748
 Carlson, C. W., 77-5994
 Carr, D. T., 77-5941
 Carroll, K. K., 77-5461
 Cartas, M. A., 77-5832
 Carter, D. M., 77-5672
 Carter, J. H., 77-5473
 Casagrande, J. T., 77-5454
 Casey, H. W., 77-5527
 Cassai, E., 77-5813, 77-5843
 Cavigneaux, A., 77-5954
 Cernea, P., 77-5666
 Cerniglia, C. E., 77-5541
 Cerny, J., 77-5860
 Cerutti, P. A., 77-5673
 Chan, J. T., 77-5421
 Chan, S. H., 77-5935
 Chan, W. C., 77-5599
 Chan, Y. P., 77-5574
 Chang, C., 77-5884
 Chang, C. C., 77-5679
 Chang, F. C., 77-5515
 Chang, R. L., 77-5560, 77-5561
 Chantepie-Auray, J., 77-5827
 Chardonnet, Y., 77-5827, 77-5828
 77-5847
 Chen, C. H., 77-5718
 Chen, H. C., 77-5859
 Chen, T. Y., 77-5824
 Cheng, L., 77-5658
 Chernozemsky, I. N., 77-5936
 Chessebeuf, M., 77-5469
 Chiang, P. K., 77-5702
 Chiazze, L., 77-5946
 Chieco-Bianchi, L., 77-5745
 Chignol, M. C., 77-5710
 Chino, F., 77-5803
 Chiou, J. F., 77-5824
 Choi, K., 77-5694
 Chopra, D. P., 77-5620
 Chopra, H. C., 77-5755
 Choquet, C., 77-5878
 Chorna, Zh. O., 77-5857
 Chortyk, O. T., 77-5596
 Chorvath, B., 77-5739
 Christian, R. T., 77-5536
 Christie, J., 77-5654
 Christoffersen, T., 77-5922
 Christopher, L. J., 77-5529
 Chu, F. S., 77-5515
 Chuprevich, T. W., 77-5628
 Cikes, M., 77-5807
 Cisowska, B., 77-5650
 Claflin, A. J., 77-5915
 Claisse, P. J., 77-5613
 Clark, E. A., 77-5887
 Clarke, S. M., 77-5893
 Clarkson, B. D., 77-5891
 Cleaver, J. E., 77-5433, 77-5795
 Cloyd, M. W., 77-5767
 Cogen, B., 77-5762
 Cohen, G. M., 77-5563
 Colapinto, V., 77-5916
 Colcher, D., 77-5776
 Cole, C. N., 77-5799
 Cole, P., 77-5417, 77-5929
 Collavo, D., 77-5745
 Collett, M. S., 77-5709
 Colombani, M. J., 77-5750
 Colombatti, A., 77-5745
 Comings, D. E., 77-5430
 Connell, J. R., 77-5630
 Connelly, R., 77-5934
 Conney, A. H., 77-5543, 77-5560
 77-5561, 77-5569
 Connor, R. J., 77-5570
 Constantinides, P. G., 77-5532
 Contesso, G., 77-5918
 Cook, G. L., 77-5504
 Coolen, J. C., 77-5849
 Corallini, A., 77-5843
 Cornhill, J. F., 77-5956
 Costanzo, F., 77-5813
 Cottrell, R. C., 77-5609
 Cotzias, G. C., 77-5992
 Couch, D. B., 77-5681
 Coulson, A., 77-5928
 Coutinho, W. G., 77-5971
 Couves, C. M., 77-5419
 Couvillion, L., 77-5884
 Craig-Holmes, A. P., 77-5627
 Craven, P., 77-5499
 Crawford, B. D., 77-5556, 77-5966
 Crecelius, E. A., 77-5641
 Crittenden, L. B., 77-5701
 Croissant, O., 77-5846
 Cronkite, E. P., 77-5655, 77-5655
 Crooks, J., 77-5529
 Cruciger, Q., 77-5908
 Crump, K. S., 77-5409
 Cueugnet, C., 77-5937
 Curling, M., 77-5530
 Dales, L. G., 77-5682
 Dambuyant, C., 77-5847
 Damjenov, I., 77-5923
 Damus, K., 77-5928
 Daniel, C. W., 77-5988, 77-5995
 Daniel, F. B., 77-5411
 Daniel, J. C., 77-5983
 Dansette, P. M., 77-5543, 77-5560
 Darai, G., 77-5812
 Darlix, J. L., 77-5700
 Darnell, J. E., 77-5831, 77-5838
 Davidson, J. F., 77-5529
 Davies, J. N., 77-5945
 Davies, P., 77-5593, 77-5595
 Davis, M. T., 77-5411
 Day, N. E., 77-5935, 77-5940
 de Lajartre, M., 77-5952
 de Saint-Maur, P. P., 77-5926
 de-The, G., 77-5423
 de The, G. B., 77-5823
 de Waard-Kuiper, E. H., 77-5875
 Deak, B., 77-5736, 77-5737
 Deal, K. L., 77-5409
 DeAngelo, A. B., 77-5576
 DeBoer, D. J., 77-5892
 Dehner, L. P., 77-5653
 Deichman, G. I., 77-5794
 Deinhardt, 77-5808
 Deinhardt, F., 77-5779
 Dekegel, D., 77-5853
 Delarue, J. C., 77-5918
 Delort-Laval, J., 77-5512
 Delplace, Y., 77-5954
 Denisova, E. A., 77-5691
 Denner, I., 77-5727
 DeRubertis, F. R., 77-5499
 Desgranges, C., 77-5823
 Deshayes, L., 77-5721
 Devare, S. G., 77-5721
 Devine, C., 77-5832
 Dewaele, J., 77-5661
 Deys, B. F., 77-5959
 Di Mayorca, G., 77-5807
 Diamond, L., 77-5760
 Dietz, M., 77-5731
 Digiovanni, J., 77-5548
 DiGuilio, W., 77-5687
 Dilawari, J., 77-5476
 DiPaolo, J. A., 77-5773
 Dipple, A., 77-5581
 Djaldetti, M., 77-5898
 Dmochowski, L., 77-5852
 Dock, D. S., 77-5692
 Doniach, I., 77-5530
 Donovan, G., 77-5854, 77-5855
 Dore, J. F., 77-5738, 77-5878
 Dotson, L., 77-5690
 Douglas, C. J., 77-5976
 Douglas, R., 77-5687
 Dowdle, J. A., 77-5653
 Downey, K. M., 77-5535
 Drohan, W., 77-5776
 Dube, D. K., 77-5634
 Dumitrescu, R., 77-5855
 Dumont, C. R., 77-5496
 Dunn, A. R., 77-5804
 Duplan, J. F., 77-5735, 77-5738
 Dupont, B., 77-5879
 Duprez, V., 77-5750
 Durmishidze, S. V., 77-5551
 Dusserre, P., 77-5937
 Dzhokhadze, D. I., 77-5551
 Eads, W., 77-5682
 Ebina, T., 77-5905
 Eckhart, W., 77-5762
 Eder, E., 77-5488
 Edwards, G. S., 77-5508
 Edwards, I., 77-5816
 Eisinger, M., 77-5845
 El Etrey, M. F., 77-5523
 Elindar, C. G., 77-5947
 Ellsworth, R. M., 77-5879
 Embree, J. W., 77-5489
 Emmelot, P., 77-5981
 Enami, J., 77-5754
 Endtz, L. J., 77-5901
 Eng, C. P., 77-5867
 Engel, E., 77-5593
 Enterline, P. E., 77-5636
 Epler, G. R., 77-5645

- Erfle, V., 77-5764
 Erskine, Z. G., 77-5529
 Essex, M., 77-5892
 Esumi, H., 77-5606
 Evans, A., 77-5457
 Evans, D. H., 77-5916
 Evans, I., 77-5985
 Evege, E., 77-5888
 Eveson, J. W., 77-5624
 Exillie, M. F., 77-5469
 Exon, J. H., 77-5873
 Fadei, L., 77-5855
 Fairbanks, L., 77-5718
 Faivre, J., 77-5937
 Faivre, M., 77-5937
 Falcieri, E., 77-5819
 Falk, L. A., 77-5808
 Faller, D. V., 77-5768
 Farber, E., 77-5920
 Farishian, R. A., 77-5986
 Farris, T., 77-5908
 Farwell, D. C., 77-5991
 Faucon, N., 77-5827, 77-5828
 Favre, M., 77-5846
 Fel', V. Ia., 77-5482
 Feldman, J. D., 77-5874
 Feldman, M., 77-5871
 Fellous, M., 77-5877
 Fenoglio, J. J., 77-5924
 Ferrando, R., 77-5492, 77-5512
 Festen, J. J., 77-5875
 Fialkow, P. J., 77-5446
 Figueras, A., 77-5579
 Fink-Bennett, D., 77-5687
 Fink, L. M., 77-5893
 Fischer, S. M., 77-5538
 Fischinger, P. J., 77-5744
 Fisher, M. S., 77-5856
 Fitzell, D. L., 77-5509
 Fjelde, A., 77-5888
 Fletcher, R. D., 77-5974
 Flugel, R. M., 77-5812
 Foa-Tomasi, L., 77-5813
 Fogh, H., 77-5906
 Fogh, J., 77-5906
 Fogh, J. M., 77-5906
 Fong, Y. Y., 77-5599
 Foster, R. S., 77-5740
 Fouchey, S. P., 77-5731
 Fourlon, C., 77-5492
 Fowler, B. A., 77-5642, 77-5643
 Fox, R. A., 77-5972
 Frank, A. L., 77-5646
 Frankel, A. E., 77-5744
 Franklin, S. G., 77-5730
 Frattola, L., 77-5993
 Fraumeni, J. F., 77-5689, 77-5931
 77-5932, 77-5950
 Freeman, A. I., 77-5899
 Freeman, H. J., 77-5894
 Freier, S. M., 77-5633
 Freudenthal, R. I., 77-5566
 Fridman, W. H., 77-5877
 Friedlos, F., 77-5582
 Friedman, G. D., 77-5682
 Friedman, H., 77-5861
 Friedman, R. D., 77-5977
 Friedman, R. M., 77-5805
 Friedrich, T. D., 77-5793
 Fries, G. F., 77-5486
 Fry, J. R., 77-5533
 Fry, R. J., 77-5671, 77-5674
 Fuji, H., 77-5862
 Fujimura, S., 77-5467
 Fukami, A., 77-5930
 Furmanski, P., 77-5731
 Gaensler, E. A., 77-5645
 Gaevaia, T. Ia., 77-5552
 Gafter, U., 77-5898
 Gak, J. C., 77-5492
 Galea, V., 77-5513
 Galil-Ogly, G. A., 77-5925
 Gallie, B. L., 77-5879
 Gallo, R. C., 77-5773
 Gallon, S. C., 77-5529
 Gamble, J., 77-5496
 Gangolli, S. D., 77-5609
 Gantt, J. S., 77-5474
 Gardner, M. B., 77-5715
 Garfinkel, L., 77-5953
 Garibian, D. Kh., 77-5597
 Garrett, T. J., 77-5891
 Garrison, A. W., 77-5403
 Gaucher, P., 77-5952
 Geard, C. R., 77-5696
 Geil, R. G., 77-5521, 77-5527
 Gelboin, H. V., 77-5562, 77-5570
 Gemmell, A., 77-5697
 Gemmell, D. S., 77-5697
 Gerkins, V. R., 77-5454
 Gerlier, D., 77-5738
 Gershbein, L. L., 77-5516
 Gerwin, B. I., 77-5741
 Gibson, D. T., 77-5541
 Gibson, W., 77-5762
 Gilbert, F., 77-5902
 Gilbert, J. H., 77-5744
 Gilbertson, J. R., 77-5974
 Gilden, R. V., 77-5583, 77-5721
 Giles, R. C., 77-5527
 Ginzton, N., 77-5736
 Giraldo, G., 77-5807
 Girard, M., 77-5791
 Gisser, S. D., 77-5912
 Glaser, M., 77-5706
 Glass, G. B., 77-5451
 Glatt, H., 77-5542
 Gliniski, W., 77-5670
 Gluck, D., 77-5677
 Goff, S. P., 77-5799, 77-5800
 Gold, B., 77-5605
 Goldberg, S., 77-5838
 Goldman, P., 77-5473
 Goldsmith, J. R., 77-5948
 Gomard, E., 77-5750
 Goni, J., 77-5647
 Good, R. A., 77-5879
 Goodman, J. W., 77-5876
 Gorbarenko, N. I., 77-5691
 Gorbunova, L. V., 77-5622
 Gordon, M., 77-5784
 Gorlin, R. J., 77-5439
 Gormus, R., 77-5997
 Goto, M., 77-5463
 Gough, B. J., 77-5517
 Goutner, A., 77-5878, 77-5896
 Goyings, L. S., 77-5522
 Graham, F. L., 77-5815
 Graham, S., 77-5955
 Graillet, C., 77-5492
 Grandjean, C., 77-5605
 Granlund, D. J., 77-5822, 77-5934
 Grant, C. K., 77-5892
 Grantham, P. H., 77-5466
 Grasso, R. J., 77-5987
 Greaves, M., 77-5878
 Green, M., 77-5832, 77-5989
 Greenland, S., 77-5928
 Greenland, T., 77-5711
 Greenwald, P., 77-5945
 Gribova, I. A., 77-5691
 Griffin, A. C., 77-5480
 Grinwich, K. D., 77-5860
 Grodzicker, T., 77-5835
 Gross, P., 77-5644
 Grossberg, A. L., 77-5862
 Grover, P. L., 77-5580
 Grube, D. D., 77-5671, 77-5674
 Grudziniskas, J. G., 77-5530
 Grunberger, D., 77-5468
 Grussendorf, E. I., 77-5844
 Grzeskowiak, K., 77-5568
 Gschnait, F., 77-5669
 Gub'skii, Iu. I., 77-5546
 Gub'skii, Iu. I., 77-5547
 Guerinot, F., 77-5918
 Guess, H. A., 77-5409
 Guillemain, B., 77-5719, 77-5735
 77-5738
 Guinn, G. A., 77-5590
 Guirgis, H. A., 77-5904
 Gundberg, C. M., 77-5814
 Gunzel, P., 77-5523
 Gurtoo, H. L., 77-5588
 Gus'kova, A. K., 77-5691
 Gusdon, J. P., 77-5816
 Gushchin, V. A., 77-5501, 77-5961
 Gyorkey, F., 77-5608
 Gyorkey, P., 77-5608
 Haapala, D. K., 77-5751
 Hadaway, E. I., 77-5576
 Hagedorn, M., 77-5640
 Hagenbeek, A., 77-5575
 Haglid, K. G., 77-5615
 Haines, A., 77-5476
 Halbrecht, I., 77-5898
 Hale, A. H., 77-5706
 Hall, L., 77-5731
 Hamajima, K., 77-5859
 Hammarstrom, S., 77-5889
 Hammond, E. C., 77-5953
 Harbell, J. W., 77-5995
 Harewood, K., 77-5777
 Harewood, K. R., 77-5775
 Harnaha, J. B., 77-5867
 Harnden, D. G., 77-5435
 Harper, P., 77-5945
 Harris, C., 77-5568

- Harris, C. C., 77-5570, 77-5603
 Harris, L. F., 77-5890
 Harris, R. E., 77-5904
 Harshbarger, J. C., 77-5404
 Hart, R. W., 77-5411, 77-5679
 Harvey, R. G., 77-5545, 77-5568
 Hassell, J. A., 77-5804
 Hata, R., 77-5747
 Hattori, M., 77-5463
 Haugen, A., 77-5615
 Hayman, E. G., 77-5725
 Hayner, N. T., 77-5588
 Hays, S., 77-5411
 Hayward, W. S., 77-5705
 Hazlewood, C. F., 77-5960
 Heath, C. W., 77-5496
 Heberling, R. L., 77-5781
 Hecht, F., 77-5438
 Hegazy, M. R., 77-5847
 Hehlmann, R., 77-5764
 Heidelberger, C., 77-5539
 Hellman, L., 77-5577
 Hellstrom, I., 77-5886
 Hellstrom, K. E., 77-5886
 Helmke, R. J., 77-5781
 Helton, E. D., 77-5517
 Henderson, B. E., 77-5454, 77-5951
 Henderson, V., 77-5636
 Hendricks, J. D., 77-5406, 77-5506
 Henle, G., 77-5825
 Henle, W., 77-5825
 Henning, C. B., 77-5697
 Hennings, H., 77-5540
 Henry, N., 77-5512
 Henschler, D., 77-5488
 Heppleston, A. G., 77-5660
 Herbst, E. J., 77-5991
 Herbst, G., 77-5816
 Hernandez-Nieto, L., 77-5921
 Hernandez, O., 77-5560
 Heston, W. E., 77-5429, 77-5752
 77-5755
 Heubner, R. J., 77-5583
 Hickok, D. F., 77-5890
 Higgins, J., 77-5892
 Higgins, P. J., 77-5919
 Higman, E. B., 77-5596
 Hilf, R., 77-5578
 Hince, T. A., 77-5612
 Hinuma, Y., 77-5859
 Hirayama, T., 77-5824
 Hirsch, G. P., 77-5680
 Hirshaut, Y., 77-5881
 Hjelmeland, L. M., 77-5491
 Hlubinova, K., 77-5739
 Hodge, V. F., 77-5658
 Hoffman, J., 77-5909
 Hogan, T. F., 77-5842
 Holliday, R., 77-5965
 Hollinger, F. B., 77-5608
 Homburg, C., 77-5981
 Honda, M., 77-5479
 Hoover, E. A., 77-5717
 Hopkins, N., 77-5768
 Horacek, J., 77-5667
 Hori, M., 77-5930
 Horwitz, M. S., 77-5839
 Howard, J. M., 77-5449
 Howe, C. C., 77-5789
 Howse, H. D., 77-5958
 Hsia, M. T., 77-5505
 Hsie, A. W., 77-5680, 77-5681
 Hsieh, D. P., 77-5509, 77-5510
 Hsu, W. T., 77-5545
 Huber, G., 77-5593, 77-5595
 Huberman, E., 77-5562
 Hudson, H. T., 77-5678
 Huebner, R. J., 77-5749
 Huesgen, A., 77-5810
 Huhtanen, C. N., 77-5514
 Huisingh, J. L., 77-5410
 Hull, D. R., 77-5675
 Hulse, E. V., 77-5685
 Hultberg, B., 77-5573
 Humes, J. L., 77-5746
 Hundley, S. G., 77-5566
 Hunter, T., 77-5762, 77-5802
 Huschtscha, L. I., 77-5965
 Hussey, J., 77-5842
 Hustin, J., 77-5520
 Hutcheson, D. P., 77-5502
 Hutton, J. J., 77-5592
 Hutzinger, O., 77-5484
 Iijima, K., 77-5858
 Inada, T., 77-5724
 Inbar, M., 77-5998
 Ingelfinger, J. A., 77-5473
 Inhorn, S. L., 77-5628
 Ioannides, C., 77-5485
 Irving, C. C., 77-5976
 Ishida, N., 77-5905
 Israel, E., 77-5708
 Ivanov, V. A., 77-5482
 Izquierdo, J. N., 77-5572
 Jablonska, S., 77-5670
 Jackson, S., 77-5659
 Jacobs, D. W., 77-5924
 Jacobs, M. M., 77-5480
 Jacobson, B. E., 77-5625
 Janowski, M., 77-5735
 Janss, D. H., 77-5576
 Jao, W., 77-5917
 Jarzabek-Chorzelska, M., 77-5670
 Jasmin, C., 77-5666
 Jasmin, J. R., 77-5666
 Jaurand, M. C., 77-5647
 Jay, F. T., 77-5805
 Jay, G., 77-5805
 Jeffrey, A. M., 77-5568
 Jelinek, W., 77-5831
 Jennette, K. W., 77-5568
 Jerina, D. M., 77-5543, 77-5560
 77-5561
 Jessup, J. M., 77-5856
 Jing, J. S., 77-5951
 Johnson, C. E., 77-5987
 Johnson, D. E., 77-5852
 Johnston, J. D., 77-5882
 Joint Iran-International Agency for Research on Cancer Study Group
 77-5940
 Jones, L. A., 77-5524
 Jones, P. A., 77-5532
 Jones, R. T., 77-5570
 Jordan, G. L., 77-5449
 Joshi, S. R., 77-5611
 Juchau, M. R., 77-5465, 77-5548
 Judson, S. C., 77-5825
 Junqua, S., 77-5661
 Kadlubar, F. F., 77-5472
 Kahan, A. V., 77-5978
 Kahan, B. D., 77-5970, 77-5978
 Kajitani, T., 77-5930
 Kakimoto, K., 77-5862
 Kakizoe, T., 77-5606
 Kalisher, L., 77-5929
 Kalter, S. S., 77-5781
 Kamo, I., 77-5861
 Kantor, G. J., 77-5675
 Kapitulnik, J., 77-5543, 77-5569
 Kaplan, H. S., 77-5871
 Kaplan, L. M., 77-5839
 Karazas, N. V., 77-5698
 Karki, N. T., 77-5553
 Kashkina, L. M., 77-5794
 Kaslow, H. D., 77-5953
 Kasumi, F., 77-5930
 Katz, E., 77-5634
 Katz, M. L., 77-5631
 Kaufman, D. G., 77-5868
 Kawachi, T., 77-5606
 Kawalek, J. C., 77-5554
 Kawamura, A., 77-5824, 77-5859
 Kayibanda, B., 77-5878, 77-5896
 Kazmer, S., 77-5631
 Keane, M. A., 77-5718
 Kedinger, C., 77-5840
 Keefer, L. K., 77-5611
 Keller, A. Z., 77-5943
 Kelley, S. P., 77-5576
 Kelly, H., 77-5528
 Kennedy, A. R., 77-5656, 77-5657
 Kesava Rao, K. V., 77-5996
 Keshet, E., 77-5714
 Kessler, I., 77-5457
 Khan, A. S., 77-5716
 Khandekar, J. D., 77-5690
 Khare, A. G., 77-5900
 Khesina, A. Ia., 77-5552
 Khoury, G., 77-5785
 Kim, C. M., 77-5749
 Kim, Y. S., 77-5450
 Kimbrough, R. D., 77-5486
 King, H. W., 77-5584
 Kirchner, R. F., 77-5491
 Kirkland, D. J., 77-5582
 Kirkwood, T. B., 77-5965
 Kirsanova, G. I., 77-5691
 Kirsten, W. H., 77-5811
 Kish, M. L., 77-5821
 Kitchen, F. D., 77-5879
 Kitchingman, G. R., 77-5837
 Klein, B., 77-5666, 77-5898
 Kleinman, R. E., 77-5839
 Klepping, C., 77-5937
 Klessig, D. F., 77-5833, 77-5833
 Klimashevskii, V. F., 77-5501
 Klimashevsky, V. F., 77-5961

- Kluchareva, T. E., 77-5794
 Kneale, G. W., 77-5683
 Knish, W. M., 77-5811
 Knox, J. M., 77-5678
 Kociba, R. J., 77-5644
 Koi, M., 77-5905
 Kolesnichenko, T. S., 77-5619
 Koller, L. D., 77-5873
 Kondo, Y., 77-5858
 Kondrat'eva, A. F., 77-5478
 Kono, N., 77-5664
 Konrad, K., 77-5669
 Korosteleva, T. A., 77-5478
 Korsgaard, R., 77-5589
 Kos, W. L., 77-5534
 Krakower, J. M., 77-5778
 Kraybill, H. F., 77-5402
 Kripke, M. L., 77-5856, 77-5872
 Krsmanovic, V., 77-5711
 Kruger, F. W., 77-5607
 Krulik, M., 77-5926
 Krylov, L. M., 77-5925
 Kryukova, I. N., 77-5851
 Krzeminski, L. F., 77-5522
 Kubo, A., 77-5467
 Kucera, L. S., 77-5816
 Kuettner, K. E., 77-5983
 Kufe, D., 77-5757
 Kuma kura, K., 77-5993
 Kuno, K., 77-5930
 Kurland, L. T., 77-5941
 Kurth, R., 77-5810
 Kuster, J. M., 77-5884
 Kuwabara, N., 77-5462
 Kwapien, R. P., 77-5527
 L'vovskaia, E. N., 77-5691
 Laerum, O. D., 77-5615
 Lai, S. P., 77-5837
 Laissue, J. A., 77-5655, 77-5655
 Lake, B. G., 77-5609
 Lallemant, C., 77-5469
 Lamar, J. K., 77-5521
 Lamb, J. C., 77-5518
 Lambert, B., 77-5668
 Land, C. E., 77-5694
 Landers, T., 77-5799
 Langner, A., 77-5670
 Lankas, G. R., 77-5536, 77-5537
 Lanko, N. S., 77-5500
 Lasfargues, E. Y., 77-5971
 Latourette, H., 77-5654
 Lauderdale, J. W., 77-5522
 Laurent, J. C., 77-5711
 Laval, J., 77-5990
 Law, L. W., 77-5885
 Lea, M. A., 77-5565
 Leavitt, J. C., 77-5966
 Lecomte, D., 77-5926
 Lee, M. Y., 77-5535
 Lee, R., 77-5850
 Lee, Y. S., 77-5818
 Legendre, N., 77-5661
 Legoux, J. L., 77-5937
 LeGrue, S., 77-5978
 Lehman, J. M., 77-5783, 77-5793
 Lejeune, F. J., 77-5853
 Lennox, E., 77-5869
 Lerer, T. J., 77-5938
 Leutz, J. C., 77-5570
 Levin, J. G., 77-5741
 Levin, W., 77-5543, 77-5554, 77-5560
 77-5561
 Levine, A., 77-5687
 Levine, A. S., 77-5805
 Levine, P. H., 77-5934
 Levine, W. G., 77-5531
 Levy, D., 77-5719, 77-5721
 Levy, J. P., 77-5721, 77-5750
 Levy, S. B., 77-5730
 Lewin, R. A., 77-5658
 Lewis, J. B., 77-5830
 Lewis, N. J., 77-5411
 Ley, R. D., 77-5671, 77-5674
 Lhoest, G., 77-5471
 Li, F. P., 77-5442
 Li, Y., 77-5823
 Libbey, L. M., 77-5507
 Liberatore, F., 77-5945
 Lichti, U., 77-5540
 Liddle, J. A., 77-5486
 Lieber, M. R., 77-5538
 Lieberman, M., 77-5736, 77-5737
 Lijinsky, W., 77-5600, 77-5602
 Lin, E. J., 77-5545
 Lin, P. J., 77-5824
 Lin, T. M., 77-5824
 Lin, Y. N., 77-5474
 Lindeberg, T. Ia., 77-5704
 Liniecki, J., 77-5650
 Linke, H., 77-5802
 Linnik, A. B., 77-5552
 Liteanu, D., 77-5853
 Little, J. B., 77-5656, 77-5657, 77-5684
 Liu, P. I., 77-5694
 Livingston, D. M., 77-5801
 Livnat, E. J., 77-5917
 Lloyd, A. G., 77-5609
 Lloyd, E. L., 77-5697
 Lober, G., 77-5420
 Loeb, L. A., 77-5634
 Loew, G. H., 77-5491
 Lofgreen, J. S., 77-5856
 London, M., 77-5676
 Longley, C., 77-5731
 Loper, J. C., 77-5494
 Lord, B. I., 77-5964
 Lotem, J., 77-5963
 Loutit, J. F., 77-5663
 Loveland, P. M., 77-5507
 Loveless, J., 77-5906
 Lovelock, J. E., 77-5418
 Lowdin, P. O., 77-5432
 Lu, A. Y., 77-5543, 77-5554, 77-5555
 Luss, E. V., 77-5622
 Lutzner, M. A., 77-5434
 Luz, A., 77-5764
 Lynch, H. T., 77-5904
 Lynch, J. F., 77-5904
 Lynch, P. M., 77-5904
 MacDonald, D. G., 77-5624
 Machanoff, R., 77-5680, 77-5681
 MacSween, J. M., 77-5972
 MacSween, R. N., 77-5944
 Mager, R., 77-5562
 Magnus, K., 77-5942
 Mah, H. D., 77-5560
 Mahboubi, E., 77-5459, 77-5525
 Mahoney, A. D., 77-5913
 Malan, L. B., 77-5576
 Malcolm, A. R., 77-5632
 Malenkov, A. G., 77-5498
 Malinin, T. I., 77-5915
 Mamoun, R., 77-5719, 77-5735
 Mandel, E. M., 77-5898
 Mandema, E., 77-5875
 Mann, K., 77-5802
 Manousos, M., 77-5775
 Manteuil-Brutlag, S., 77-5799
 Manuelidis, E. E., 77-5766
 Manuelidis, L., 77-5766
 Marefat, P., 77-5571
 Margison, G. P., 77-5616
 Marquardt, H., 77-5580, 77-5601
 Marquart, K. H., 77-5764
 Marrink, J., 77-5875
 Marshak, M. I., 77-5622
 Martin, F., 77-5937
 Martin, M. A., 77-5806
 Martin, R. F., 77-5761
 Martin, R. G., 77-5801
 Martin, R. R., 77-5590, 77-5591
 Marty, L., 77-5791
 Marusic, M., 77-5876
 Marzulli, F. N., 77-5670
 Mason, T., 77-5718
 Masse, R., 77-5661
 Mathes, L. E., 77-5717
 Mathews, M. B., 77-5835
 Matsushima, T., 77-5479
 Matsuzawa, A., 77-5497
 Mattiasson, I., 77-5589
 Mattox, K. L., 77-5590
 May, E., 77-5785
 May-Levin, F., 77-5918
 Mayer, A. M., 77-5864, 77-5866
 Mayer, D., 77-5614
 Mayyasi, S. A., 77-5775
 Maziere, C., 77-5782
 Maziere, J. C., 77-5782
 McAllister, H. A., 77-5924
 McAllister, P. E., 77-5426
 McBride, R. A., 77-5865
 McCance, D. J., 77-5759
 McCaw, B. K., 77-5438
 McCormick, K. J., 77-5723
 McDevitt, H. O., 77-5736, 77-5737
 McDowell, E., 77-5570
 McDowell, E. M., 77-5603
 McFarland, V. M., 77-5884
 McGandy, R. B., 77-5657
 McGrath, C. M., 77-5756
 McGrath, M., 77-5707
 McGregor, D. H., 77-5694
 McInnes, J., 77-5989
 McKeen, E. A., 77-5903
 McLachlan, J. A., 77-5518
 McLemore, T. L., 77-5590, 77-5591
 Mearns, A. J., 77-5407

- Medline, A., 77-5920
 Meek, R. L., 77-5988
 Mehrishi, J. N., 77-5663
 Meisner, L. F., 77-5628
 Melnick, J. L., 77-5608
 Memik, F., 77-5939
 Menck, H. R., 77-5951
 Mercier, M., 77-5471
 Meruelo, D., 77-5736, 77-5737
 Metivier, H., 77-5661
 Metz, G., 77-5476
 Metzler, M., 77-5488
 Michaelson, S., 77-5686
 Michiels, R., 77-5937
 Miguez, J. B., 77-5991
 Milder, D., 77-5906
 Miller, E. C., 77-5472
 Miller, G. A., 77-5874
 Miller, J. A., 77-5472
 Miller, J. M., 77-5687
 Miller, L. L., 77-5890
 Miller, R. W., 77-5444, 77-5456
 77-5458
 Mims, C. A., 77-5759
 Minegishi, K., 77-5477
 Minna, J. D., 77-5428
 Minowada, J., 77-5588
 Mirkovic, G. A., 77-5608
 Mirza, A., 77-5829
 Mischynski, M., 77-5928
 Mitchell, J. R., 77-5933
 Mitelman, F., 77-5573
 Miyaki, M., 77-5623
 Mizuno, Y., 77-5497
 Mochizuki, Y., 77-5481
 Modan, B., 77-5460, 77-5688
 Modianova, E. A., 77-5498
 Moghissi, K. S., 77-5413
 Mohn, G. R., 77-5511
 Mohr, U., 77-5607
 Moir, D. C., 77-5529
 Moldow, C. F., 77-5707, 77-5897
 77-5997
 Mollner, T., 77-5483
 Mondal, S., 77-5539
 Montagnier, L., 77-5774
 Montesano, R., 77-5616
 Moolten, D. N., 77-5618
 Moolten, F. L., 77-5618
 Moore, B. P., 77-5563
 Moore, C., 77-5834
 Moorhead, E. L., 77-5689
 Mora, P. T., 77-5884
 Morahan, P. S., 77-5729
 Morecki, R., 77-5543
 Morgan, D. G., 77-5809
 Morin, M., 77-5666
 Morita, K., 77-5858
 Moroni, C., 77-5769
 Morse, L. S., 77-5817
 Motell, E. L., 77-5509
 Mougeot-Martin, M., 77-5926
 Mountain, I. M., 77-5577
 Mueller, S. N., 77-5587
 Mulligan, L. T., 77-5610
 Mulvihill, J. J., 77-5436, 77-5903
 Munk, K., 77-5812
 Murata, M., 77-5859
 Mushinski, M. H., 77-5416
 N'Diaye, A. L., 77-5512
 Naccarato, W. F., 77-5974
 Nachtomi, E., 77-5487
 Nagabayashi, T., 77-5426
 Nagao, M., 77-5479
 Nagumo, F., 77-5858
 Nakamura, K., 77-5693
 Nakanishi, K., 77-5568
 Namkung, M. J., 77-5465
 Nance, W. E., 77-5443
 Nandi, S., 77-5754
 Nannestad-Hansen, F., 77-5999
 Naso, R. B., 77-5726
 Natori, T., 77-5885
 Nelson, L. W., 77-5526
 Nemoto, N., 77-5564
 Nenci, L., 77-5843
 Nepom, J. T., 77-5886
 Neudecker, T., 77-5488
 Neulist, L., 77-5690
 Newbold, R. R., 77-5518
 Nexo, B. A., 77-5765
 Nicholas, H., 77-5595
 Nicholls, D. M., 77-5574
 Nichols, W. E., 77-5946
 Nicholson, W., 77-5417
 Niesor, E., 77-5788
 Nigro, N. D., 77-5474
 Nikolov, I. G., 77-5936
 Nikonova, T. V., 77-5550
 Niman, H. L., 77-5715
 Nixon, J. E., 77-5507
 Nonoyama, M., 77-5818
 Noonan, K. D., 77-5979
 Nooter, K., 77-5849
 Norbury, K. C., 77-5872
 Nordenson, I., 77-5639
 Norris, J. M., 77-5644
 Nygaard, O. F., 77-5625
 O'Brien, T. G., 77-5760
 O'Neill, J. P., 77-5680, 77-5681
 Occupational Safety and Health Administration, 77-5949
 Ockey, C. H., 77-5630
 Oesch, F., 77-5542
 Ogawa, K., 77-5920
 Ogden, J., 77-5808
 Ohkubo, M., 77-5467
 Ohsawa, N., 77-5858
 Ohta, G., 77-5664
 Ohtsuki, Y., 77-5852
 Okada, S., 77-5649
 Okano, G., 77-5481
 Okazaki, W., 77-5701
 Okigaki, T., 77-5749
 Okun, J. D., 77-5604
 Okuyama, A., 77-5989
 Old, L. J., 77-5891
 Oldbring, J., 77-5589
 Olenov, Iu. M., 77-5482
 Olsen, R. G., 77-5717
 Olson, C., 77-5722, 77-5883
 Onda, H., 77-5982
 Ong, T. M., 77-5511
 Ono, T., 77-5623
 Onuma, M., 77-5722, 77-5883
 Orchin, M., 77-5567
 Ord, M. G., 77-5531
 Orser, B., 77-5718
 Orth, G., 77-5845, 77-5846
 Osato, T., 77-5820
 Osborne, M. R., 77-5584
 Oshima, R. G., 77-5792
 Oshimura, M., 77-5899
 Osman, S. F., 77-5514
 Osono, M., 77-5859
 Ostertag, W., 77-5733, 77-5734
 Otake, M., 77-5692
 Overstreet, R. M., 77-5958
 Owens, D. W., 77-5678
 Oyasu, R., 77-5978
 Padgett, B. L., 77-5842
 Padieu, P., 77-5469
 Pai, S. R., 77-5996
 Paigen, B., 77-5588
 Pal, B. K., 77-5725
 Palitti, F., 77-5629
 Palmer, F., 77-5706
 Pancirov, R. J., 77-5549
 Panem, S., 77-5811
 Pang, R. H., 77-5751
 Panigrahy, B., 77-5723
 Papas, T. S., 77-5699
 Papkoff, J. S., 77-5995
 Papoian, S. A., 77-5597
 Papworth, D. G., 77-5651
 Parke, D. V., 77-5452, 77-5485
 77-5563
 Parker, N. B., 77-5588
 Parks, V. R., 77-5953
 Parks, W. P., 77-5752
 Parodi, A., 77-5512
 Parodi, A. L., 77-5719, 77-5721
 Pasqualini, C. D., 77-5864, 77-5866
 Pass, F., 77-5845
 Pathak, S., 77-5908
 Paul, D., 77-5968
 Paul, J., 77-5733, 77-5734
 Paul, P. S., 77-5713
 Pawinska, M., 77-5670
 Pawlowski, N. E., 77-5507
 Payne, L. N., 77-5424
 Pearson, L. D., 77-5722
 Pedersen, N. C., 77-5718
 Pegg, A. E., 77-5503
 Pelgrom von Motz, I., 77-5901
 Pelkonen, O., 77-5553
 Pellet, O. L., 77-5792
 Perlmann, P., 77-5889
 Pershagen, G., 77-5947
 Persico-DiLauro, M., 77-5801
 Pessin, J. E., 77-5706
 Pestka, S., 77-5989
 Peterkofsky, B., 77-5747
 Peters, L. J., 77-5528
 Peters, R. L., 77-5583
 Peterson, A. R., 77-5539
 Peterson, C., 77-5707
 Petitou, M., 77-5998

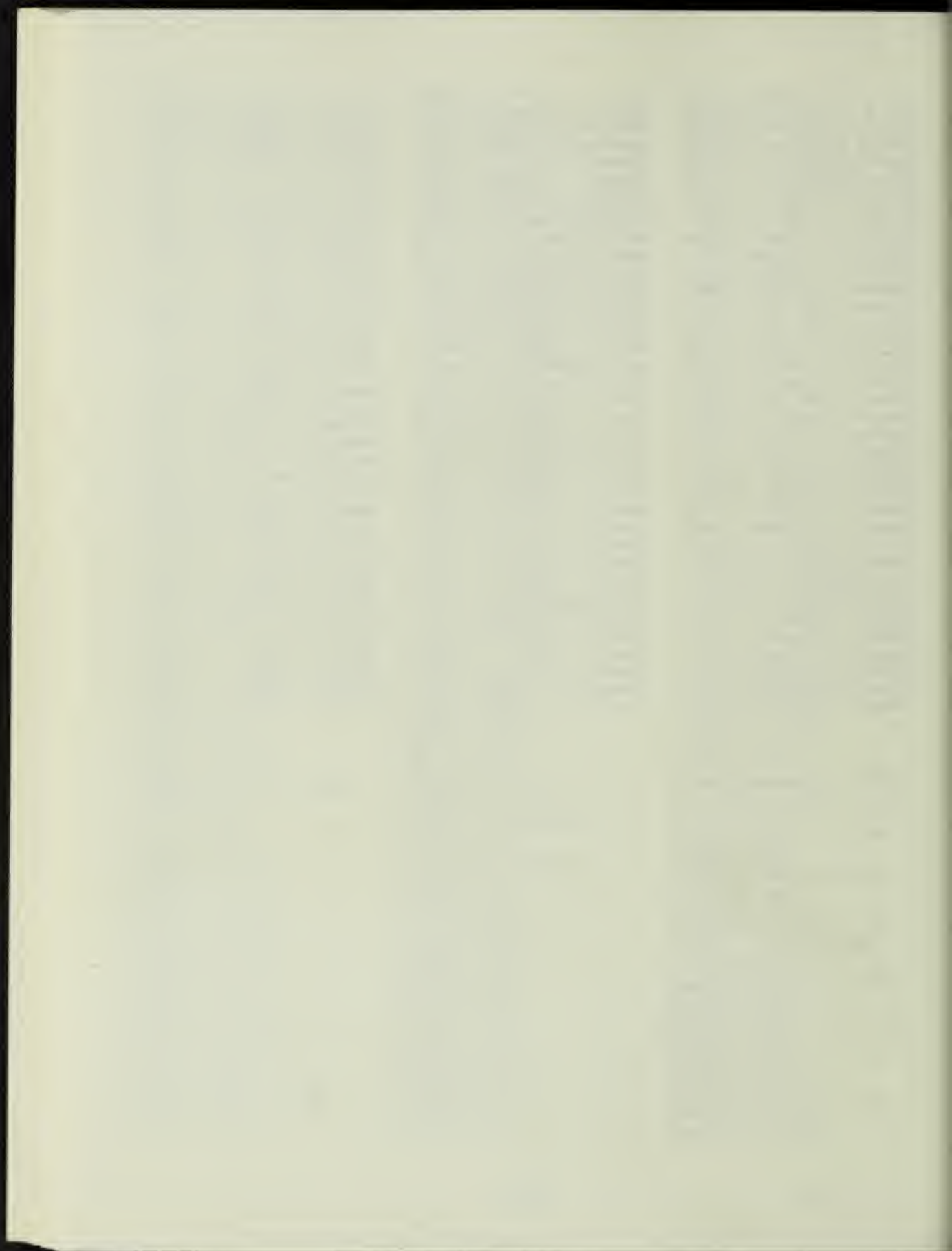
- Petrakis, N. L., 77-5455
 Petres, J., 77-5640
 Petrova-Bacharova, T., 77-5936
 Peyster, R. G., 77-5929
 Pezzuto, J. M., 77-5565
 Philipps, C., 77-5679
 Phillips, J. C., 77-5609
 Phillips, L. A., 77-5751
 Pickard, L. R., 77-5590
 Pico, J. L., 77-5878
 Piercey, J. R., 77-5894
 Pike, M. C., 77-5454, 77-5951
 Pinto, S. S., 77-5636
 Placek, V., 77-5667
 Pluzhnikova, G. F., 77-5704
 Poirier, L. A., 77-5466
 Pokras'on, M. M., 77-5547
 Polan, A., 77-5945
 Polonovski, J., 77-5782
 Pomeroy, B. S., 77-5713
 Popp, I., 77-5854, 77-5855
 Poppers, P. J., 77-5569
 Poroshin, K. K., 77-5925
 Portolani, M., 77-5843
 Posharissky, K. M., 77-5961
 Post, J., 77-5909
 Pour, P., 77-5607
 Pozharisskii, K. M., 77-5501
 Pradii, T. P., 77-5546
 Pragnell, I. B., 77-5733, 77-5734
 77-5770
 Prasad, I., 77-5760
 Pressman, D., 77-5862
 Price, M. R., 77-5427
 Price, P. J., 77-5583
 Priest, N. D., 77-5659
 Prochownik, E. V., 77-5811
 Prutkin, L., 77-5975
 Pry, T. W., 77-5699
 Pulkabek, P., 77-5468
 Putnam, G. B., 77-5406
 Putnam, T. P., 77-5506
 Putzrath, R. K., 77-5973
 Que, B. G., 77-5535
 Quinlan, W. J., 77-5686
 Radonovich, M. F., 77-5787
 Raitano, F., 77-5483
 Rajaraman, R., 77-5972
 Rajewsky, M. F., 77-5615
 Ranadive, K. J., 77-5900
 Ray, D. A., 77-5702
 Razzouk, C., 77-5471
 Reale, E., 77-5464
 Recant, W., 77-5917
 Reddick, R., 77-5689
 Redmond, C. K., 77-5938
 Reed, S. I., 77-5786
 Reese, D. H., 77-5977
 Reimer, R. R., 77-5689
 Reincke, U., 77-5655, 77-5655
 Reissig, M., 77-5845
 Reitz, M. S., 77-5773
 Reme, T., 77-5750
 Remsen, J., 77-5673
 Renold, A. E., 77-5788
 Ressang, A. A., 77-5720
 Reuber, M. D., 77-5490
 Rhim, J. S., 77-5749
 Rhode, S. L., 77-5797, 77-5798
 Rice, J. M., 77-5611
 Rich, M. A., 77-5731
 Riethmuller, G., 77-5810
 Rifa, J., 77-5579
 Roan, J. G., 77-5873
 Robb, J. A., 77-5792
 Roberfroid, M., 77-5471
 Robert, L., 77-5661
 Roberts, J. J., 77-5581, 77-5582
 Roberts, R. M., 77-5979
 Robertson, K. A., 77-5505
 Robinson, L., 77-5923
 Robinson, O. R., 77-5728
 Roessner, A., 77-5621
 Rogers, A. E., 77-5466
 Rogers, K. J., 77-5503
 Rohrer, T., 77-5955
 Roizman, B., 77-5817
 Roller, P. P., 77-5611
 Rommelaere, J., 77-5768
 Ron, E., 77-5688
 Roscoe, J. P., 77-5612, 77-5613
 Rosenberg, B. J., 77-5577
 Rosenfeld, C., 77-5878, 77-5896
 77-5998
 Rossman, T., 77-5975
 Roszell, J. A., 77-5976
 Roth, D., 77-5676
 Roussel, M., 77-5712
 Rowley, J. D., 77-5431
 Roy-Burman, P., 77-5715, 77-5725
 Rozman, C., 77-5921
 Rudolph, A. H., 77-5678
 Rufino, F., 77-5601
 Rutzky, L. P., 77-5970, 77-5978
 Ryan, D., 77-5554
 Saal, J. G., 77-5810
 Sachs, L., 77-5562, 77-5963
 Sairenji, T., 77-5859
 Saito, Y., 77-5859
 Sakamoto, G., 77-5930
 Sakurai, M., 77-5858
 Salhab, A. S., 77-5508
 Salzman, N. P., 77-5787
 Sambrook, J., 77-5835
 San Sebastian, J. R., 77-5681
 Sandberg, A. A., 77-5899
 Sarma, D. S., 77-5487
 Sato, N., 77-5858
 Sautter, J. H., 77-5713
 Saxinger, W. C., 77-5773
 Schachner, M., 77-5615
 Schafer, M. P., 77-5699
 Schafer, P., 77-5603
 Schafer, W., 77-5779, 77-5810
 Schaffer, P. A., 77-5817
 Schaller, J. P., 77-5717
 Scheuer, P. J., 77-5944
 Schidlovsky, G., 77-5775
 Schierman, L. W., 77-5865
 Schiller, C. M., 77-5642, 77-5643
 Schimke, R. N., 77-5447
 Schlake, W., 77-5621
 Schlatter, C., 77-5408
 Schloen, L., 77-5807
 Schlom, J., 77-5757, 77-5776
 Schmassmann, H., 77-5542
 Schmidt, J., 77-5770
 Schmitt, D., 77-5870
 Schneider, J. A., 77-5792
 Schneiderman, M., 77-5417
 Schneewis, K. E., 77-5422
 Schochetman, G., 77-5776
 Schoental, R., 77-5414
 Schoeny, R., 77-5494
 Schull, W. J., 77-5437
 Schuller, G. B., 77-5729
 Schumann, G., 77-5769
 Schuppler, J., 77-5523
 Schwartz, D. P., 77-5514
 Schwartz, H., 77-5838
 Schwartz-Luft, E., 77-5708
 Schwartz, S. A., 77-5984
 Schwarz, H., 77-5779
 Schwarz, J. A., 77-5540
 Schwarzacher, H. G., 77-5672
 Scialy, D., 77-6000
 Scommegna, A., 77-5917
 Scott, B. R., 77-5651
 Scribner, J. D., 77-5470
 Seal, G., 77-5634
 Sebastien, P., 77-5647
 Sedita, B. A., 77-5674
 Seibles, J. C., 77-5567
 Seino, Y., 77-5479
 Selikoff, I. J., 77-5953
 Selkirk, J. K., 77-5557, 77-5570
 Seman, G., 77-5852
 Sendecki, W., 77-5574
 Senik, A., 77-5877
 Senior, A. E., 77-5578
 Setchell, M. E., 77-5530
 Sethi, J., 77-5881
 Sevc, J., 77-5667
 Severson, R. F., 77-5596
 Seymour, J. L., 77-5505
 Shabad, L. M., 77-5498
 Shabtai, F., 77-5398
 Shah, K. V., 77-5845
 Shani, M., 77-5787
 Shanmugaratnam, K., 77-5935
 Shapiro, N. I., 77-5622
 Sharma, J. M., 77-5880
 Sharp, P. A., 77-5834
 Shaw, M. W., 77-5627
 Sheehan, D. M., 77-5519
 Sheppard, J. R., 77-5997
 Sherwood, M. J., 77-5407
 Shevliaghyn, V. J., 77-5698
 Shima, I., 77-5664
 Shimizu, M., 77-5467
 Shimkin, M. B., 77-5493
 Shimojo, H., 77-5743
 Shinohara, K., 77-5673
 Shinpock, S. G., 77-5876
 Shklar, G., 77-5571
 Shnitka, T. K., 77-5894
 Shubik, P., 77-5483, 77-5525
 Sikora, K., 77-5869

- Sil'chenko, V. P., 77-5547
 Slmkovic, D., 77-5739
 Slmkovicova, M., 77-5739
 Slmmons, D. T., 77-5806
 Simons, M. J., 77-5935
 Sims, P., 77-5580
 Singer, A., 77-5453
 Singer, I. I., 77-5797, 77-5798
 Singh, D. V., 77-5474
 Singh, R., 77-5509, 77-5510
 Sinnhuber, R. O., 77-5406, 77-5506
 77-5507
 Sirover, M. A., 77-5634
 Sirsat, S. M., 77-5585
 Skachkov, A. P., 77-5478
 Sklarew, R. J., 77-5909
 Slaga, T. J., 77-5538, 77-5540, 77-5544
 77-5548, 77-5561
 Slomiany, B. L., 77-5451
 Smadja-Joffe, F., 77-5666
 Smets, L. A., 77-5980
 Smith, G. C., 77-5781
 Smith, P. G., 77-5457
 Smith, R. D., 77-5578
 So, A. G., 77-5535
 Sobels, F. H., 77-5401
 Sohis, H., 77-5914
 Soderberg, F. B., 77-5473
 Soldatova, V. A., 77-5691
 Solt, D., 77-5920
 Sonstegard, R. A., 77-5699
 Sornberger, C., 77-5595
 Soule, H. D., 77-5756
 Spahr, P. F., 77-5700
 Spano, P. F., 77-5993
 Sparschu, G. L., 77-5644
 Spencer, J. L., 77-5701
 Spivak, J. C., 77-5416
 Springer, S. T., 77-5868
 St. Vincent, L., 77-5616
 Stahl, K., 77-5621
 Staurou, D., 77-5615
 Stegens, N. L., 77-5948
 Stehelin, D., 77-5712
 Stephenson, J. R., 77-5715, 77-5716
 77-5721, 77-5772
 Stern, E., 77-5928
 Stern, P., 77-5869
 Sternberg, S. S., 77-5475
 Stevens, W., 77-5662
 Stevonkova, J., 77-5739
 Stewart, A. M., 77-5683
 Stewart, H. L., 77-5405
 Stewart, P. S., 77-5594
 Stiller, R. A., 77-5860
 Stillman, B. W., 77-5836
 Stinson, E. E., 77-5514
 Stock, C. C., 77-5577
 Stocken, L. A., 77-5531
 Stollar, B. D., 77-5730
 Stone, B. J., 77-5932, 77-5950
 Stone, D., 77-5975
 Stoneham, M. E., 77-5850
 Stonen, G., 77-5570
 Stoner, G. D., 77-5493, 77-5603
 Stover, B. J., 77-5662
 Stoyanov, I. S., 77-5936
 Stranden, E., 77-5695
 Strauss, M., 77-5796
 Stumpf, W. W., 77-5518
 Suarez, F., 77-5791
 Sudo, K., 77-5859
 Sugano, H., 77-5930
 Sugden, B., 77-5826
 Sugimura, T., 77-5479, 77-5606
 Sugiyama, K., 77-5463
 Suk, W. A., 77-5583
 Sunderman, F. W., 77-5412, 77-5635
 Suzuki, K., 77-5859
 Suzuki, N., 77-5649
 Svenberg, T., 77-5889
 Swanbeck, G., 77-5668
 Swarbrick, R. E., 77-5558
 Swartzendruber, D. E., 77-5793
 Swift, M., 77-5440
 Symons, A. M., 77-5452
 Taillemlte, J. L., 77-5926
 Takahashi, T., 77-5891
 Takayama, S., 77-5462, 77-5564
 Takemoto, K. K., 77-5806
 Takeuchi, T., 77-5606
 Tamaoki, N., 77-5858
 Tampieri, M., 77-5843
 Tan, K. B., 77-5789
 Tanaka, N., 77-5463
 Tang, L. C., 77-5992
 Tarrant, G. M., 77-5965
 Taylor, B. A., 77-5592
 Taylor, H. W., 77-5600, 77-5602
 Teller, M. N., 77-5577
 Temin, H. M., 77-5714
 Teramoto, Y. A., 77-5757
 Tewfik, F., 77-5654
 Tewfik, H., 77-5654
 Theile, M., 77-5796
 Theilen, G., 77-5718
 Theiss, J. C., 77-5493
 Thiel, H. J., 77-5779
 Thiel, J., 77-5810
 Thiele, J., 77-5464
 Thimmapaya, B., 77-5790
 Thivolet, J., 77-5847, 77-5870
 Thompson, S., 77-5544, 77-5548
 Thon, W., 77-5539
 Thorner, M. O., 77-5530
 Thyresson-Hok, M., 77-5668
 Tibbetts, C., 77-5841
 Tierney, B., 77-5580
 Ting, R. C., 77-5773
 Todaro, G. J., 77-5780
 Tokuoka, S., 77-5694
 Tomita, J. T., 77-5970
 Tomita, M., 77-5766
 Tomlin, D., 77-5592
 Tong, S., 77-5485
 Tonlolo, A., 77-5732
 Toppell, K. L., 77-5591
 Trabucchi, M., 77-5993
 Trell, E., 77-5589
 Trentin, J. J., 77-5723
 Treves, A. J., 77-5871
 Troll, D., 77-5678
 Troll, W., 77-5975
 Trosko, J. E., 77-5679
 Troye, M., 77-5889
 Truhaut, R., 77-5492
 Trump, B. F., 77-5570, 77-5603
 Ts'o, P. O., 77-5556, 77-5966
 Tsapis, A., 77-5877
 Tseng, W. P., 77-5638
 Tsuruo, T., 77-5703
 Tsuya, A., 77-5692
 Tu, S. M., 77-5824
 Tu, Y. C., 77-5824
 Tulp, M. T., 77-5484
 Tursz, T., 77-5877
 Turusov, V. S., 77-5500
 Tuy, F., 77-5998
 Uchida, Y., 77-5621
 Uetake, H., 77-5724
 Ueyama, Y., 77-5858
 Ulrich, K., 77-5765
 Umezawa, H., 77-5606
 Urquhart, C., 77-5784
 Ury, H. K., 77-5682
 Utzinger, R., 77-5408
 Uyttenbroeck, F., 77-5910
 Vaillier, D., 77-5863
 Vaillier, J., 77-5863
 Vainberg, R. M., 77-5559
 Valentova, N., 77-5739
 Van Beek, W. P., 77-5980, 77-5981
 Van den Berg, H. W., 77-5582
 Van den Eynde, J. P., 77-5520
 van Muijen, G. N., 77-5848
 Van Nest, G. A., 77-5969
 Van Nie, R., 77-5980
 Van Tlegghem, N., 77-5853
 van Veen, J., 77-5979
 Vandenbussche, P., 77-5853
 Vandeputte, M., 77-5914
 Varner, M. O., 77-5636
 Varshaver, N. B., 77-5622
 Venske, G., 77-5614
 Venuat, A. M., 77-5878
 Vercammen-Grandjean, A. F., 77-5853
 Viac, J., 77-5847, 77-5870
 Vlajic, A., 77-5540, 77-5544, 77-5548
 Vianna, N., 77-5945
 Vigier, P., 77-5710
 Viladiu, P., 77-5579
 Vlahakis, G., 77-5648, 77-5755
 Vogt, P. K., 77-5701
 Wahlund, G., 77-5889
 Walnberg, M. A., 77-5708
 Waisman, J., 77-5913
 Wakabayashi, T., 77-5694
 Wakano, Y., 77-5692
 Wales, J. H., 77-5406
 Walker, D. L., 77-5842
 Wallen, W. C., 77-5934
 Walter, G., 77-5802
 Warkany, J., 77-5448
 Warnaar, S. O., 77-5848
 Wass, J. A., 77-5530
 Watanabe, D. H., 77-5865
 Waters, M. D., 77-5410
 Waxweiler, R. J., 77-5496

Webb, S. J., 77-5850
 Weber, J., 77-5829, 77-5831
 Weber, M. J., 77-5706
 Wee, G. B., 77-5935
 Weikel, J. H., 77-5526
 Weil, R., 77-5788
 Weimann, B., 77-5770
 Weinstein, D., 77-5631
 Weinstein, I. B., 77-5468, 77-5568
 Weinstein, W. M., 77-5894
 Weir, R. D., 77-5529
 Weisburger, E. K., 77-5415, 77-5493
 Weisburger, J. H., 77-5601
 Weiss, R., 77-5425
 Weiss, S. B., 77-5545
 Weissman, S. M., 77-5790
 Wenk, M. L., 77-5611
 Wensel, R. H., 77-5894
 Werner, A., 77-5688
 West, S. B., 77-5555
 Westphal, H., 77-5837
 Weymouth, L. A., 77-5634
 Wheatley, V., 77-5975
 Wheeler, L. A., 77-5473
 Wheldon, T. E., 77-5962
 Whitsett, C., 77-5879
 Whittaker, J. R., 77-5986
 Whur, P., 77-5784
 Wideman, L., 77-5502
 Wiggins, H., 77-5476
 Wigle, D. T., 77-5957
 Wilbanks, G. D., 77-5911
 Wilhelm, J., 77-5840
 Wilkoff, L. J., 77-5620
 Williams, D. C., 77-5784
 Williams, M. L., 77-5974
 Williams, R. R., 77-5948
 Wilson, R. B., 77-5502

Winter, R. B., 77-5653
 Wintersberger, E., 77-5758
 Wintersberger, U., 77-5758
 Wiseman, F., 77-5978
 Wislocki, P. G., 77-5560
 Witter, R. L., 77-5701
 Wodzinski, S. F., 77-5987
 Wold, W. S., 77-5832
 Wolf, K., 77-5426
 Wolfe, L. G., 77-5808
 Wolff, K., 77-5669, 77-5672
 Wolff, L. H., 77-5717
 Wolff, M. S., 77-5495
 Wolff-Schreiner, E. C., 77-5672
 Woiska, H., 77-5670
 Wong, J. J., 77-5510
 Wong, L. M., 77-5524
 Wong, O., 77-5946
 Wong, P. K., 77-5742
 Wood, A. W., 77-5560, 77-5561
 Wood, G., 77-5469
 Woods, J. S., 77-5642, 77-5643
 Woolner, L. B., 77-5941
 Worley, M. B., 77-5892
 Wray, N. P., 77-5590
 Wright, E., 77-5784
 Wright, E. G., 77-5964
 Wright, E. S., 77-5419
 Wright, J., 77-5808
 Wright, W., 77-5906
 Wynder, E. L., 77-5416
 Wyszynska, K., 77-5650
 Yagi, H., 77-5560, 77-5561
 Yahagi, T., 77-5479
 Yajima, Y., 77-5818
 Yamaha, T., 77-5477
 Yamamoto, K., 77-5820
 Yamamoto, R. S., 77-5415

Yamamoto, T., 77-5497
 Yamasaki, H., 77-5468
 Yang, C. S., 77-5565, 77-5824
 Yang, H. S., 77-5604
 Yang, J., 77-5754
 Yang, N. S., 77-5756
 Yang, S. K., 77-5562, 77-5570
 Yatagai, K., 77-5623
 Young, A. E., 77-5660
 Young, B. G., 77-5821
 Young, I., 77-5912
 Young, J. L., 77-5931
 Yu, M., 77-5708
 Yuasa, Y., 77-5743
 Yuen, P. H., 77-5742
 Yunis, E. J., 77-5897
 Yuspa, S. H., 77-5540
 Zabransky, B. J., 77-5697
 Zachariah, P. K., 77-5465
 Zaldivar, R., 77-5637
 Zapol'skaia, N. A., 77-5665
 Zardi, L., 77-5616
 Zaynoun, S., 77-5669
 Zedeck, M. S., 77-5475
 Zeldis, L. J., 77-5913
 Zell, T. E., 77-5514
 Zerbini, M., 77-5819
 Zhorno, L. Ia., 77-5665
 Zhudina, A. I., 77-5704
 Zimbelman, R. G., 77-5522
 Zouzias, D., 77-5760
 Zuna, R. E., 77-5783
 Zurcher, D., 77-5849
 Zweidler, A., 77-5730
 Zwilling, B. S., 77-5868



Subject Index

Abdominal Neoplasms

- Lymphoma
 - Case Report, 77-5894
 - Histological Study, 77-5894
 - Sprue, 77-5894
- Phosphoric Acid, Titanium Salt
 - Hamster, 77-5644

Acetaldehyde, Chloro-

- DNA Repair
 - Quantitation Method, Review, 77-5411

Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-

- Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 - Water, 77-5470
- DNA
 - Binding, 77-5468

Acetamide, *N*-Fluoren-2-yl-

- Acetamide, *N*-(5-Hydroxyfluoren-2-yl)-
 - Metabolism, Rat, 77-5466
- Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 - Carcinogenic Metabolite, 77-5471
 - Metabolism, Rat, 77-5466
 - Quantitation Method, 77-5471
- Amino Acids
 - Metabolism, Rat, 77-5466
- Cells, Cultured
 - Carcinogenic Metabolite, 77-5469
- Folic Acid
 - Acetamide, *N*-(5-Hydroxyfluoren-2-yl)-, 77-5466
- Glucuronidase
 - Carcinogenic Metabolite, 77-5472
 - DNA, Binding, 77-5472
- Glutathione
 - Liver, Rat, 77-5466
- Hepatoma
 - Diethylamine, *N*-Nitroso-, 77-5920
- Hydroxylases
 - Liver, Rat, 77-5466
- Liver
 - Ultrastructural Study, 77-5922
- Liver Neoplasms
 - Immunity, 77-5427
 - Review, 77-5415
- Methionine, *S*-Adenosyl-
 - Liver, Rat, 77-5466
- Microsomes, Liver
 - Carcinogenic Metabolite, 77-5472
- Oxidoreductases
 - Liver, Rat, 77-5466
- Pancreatic Neoplasms
 - Epidemiology, Review, 77-5449
- Pyridinium, 3-(Aminocarbonyl)-1-methyl-
 - Metabolism, Rat, 77-5467
- 2-Pyridone-5-carboxamide, 1-Methyl-
 - Metabolism, Rat, 77-5467
- 4-Pyridone-5-carboxamide, 1-Methyl-
 - Metabolism, Rat, 77-5467
- Pyridones
 - Liver, Rat, 77-5467

Acetamide, *N*-Fluoren-2-yl- (cont'd)

- Metabolism, Rat, 77-5467
- Salmonella typhimurium*
 - Gastrointestinal System, Rat, 77-5473
 - Revertants, Germ-Free Rat, 77-5473
- Urine
 - Carcinogenic Metabolite, 77-5469

Acetamide, *N*-(5-Hydroxyfluoren-2-yl)-

- Acetamide, *N*-Fluoren-2-yl-
 - Folic Acid, 77-5466
 - Metabolism, Rat, 77-5466

Acetamide, *N*-(7-Hydroxyfluoren-2-yl)-

- Sulfonation
 - Carcinogenic Metabolite, 77-5465

Acetic Acid, Methylnitrosaminomethyl Ester

- Intestinal Neoplasms
 - Dose-Response Study, Rat, 77-5611
- Kidney Neoplasms
 - Dose-Response Study, Rat, 77-5611
- Lung Neoplasms
 - Dose-Response Study, Rat, 77-5611

Acetic Acid, Vinyl Ester

- Carcinogenic Potential
 - Mouse, 77-5597

Acetohydroxamic Acid, *N*-Fluoren-2-yl-

- Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 - Water, 77-5470
- Acetamide, *N*-Fluoren-2-yl-
 - Carcinogenic Metabolite, 77-5471
 - Metabolism, Rat, 77-5466
 - Quantitation Method, 77-5471
- Glucuronidase
 - Carcinogenic Metabolite, 77-5472
 - DNA, Binding, 77-5472
- Liver Neoplasms
 - Review, 77-5415
- Microsomes, Liver
 - Carcinogenic Metabolite, 77-5472
- Sulfonation
 - Carcinogenic Metabolite, 77-5465

Acid Phosphatase

- Lung Neoplasms
 - Enzymatic Activity, 77-5656
- Smoking
 - Lung, 77-5594

Acrylamide

- Adipose Tissue
 - Metabolism, Review, 77-5495

Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-

- DNA
 - Binding, 77-5463
- Mammary Neoplasms, Experimental
 - Rat, 77-5462
- Stomach Neoplasms
 - Carcinoma, Epidermoid, 77-5462
 - Food Preservatives, 77-5462
 - Mouse, 77-5462

- Actinomycin D**
 Lymphocytes
 Chromosome Aberrations, 77-5628
 Succinate Dehydrogenase
 Enzymatic Activity, 77-5546
 Virus, Murine Leukemia
 Reverse Transcriptase, 77-5741
- Adenocarcinoma**
 Adrenal Gland Neoplasms
 Asbestos, 77-5644
 Colonic Neoplasms
 Carcinoembryonic Antigen, 77-5970
 Glycoproteins, Review, 77-5450
 Lung Neoplasms
 Radiation, Ionizing, 77-5667
 Mammary Neoplasms, Experimental
 Carbamic Acid, Ethyl Ester, 77-5497
 Contraceptives, Oral, 77-5526
 Ethinerone, 77-5521
 Norgestrel, Chloroethynyl-, 77-5521
 Virus, Murine Mammary Tumor, 77-5755
 Nickel
 Rat, 77-5635
 Nose Neoplasms
 Epidemiology, 77-5950
 Preg-4-en-20-one, 17-(Acetyloxy)-6 α -methyl-
 Mammary Neoplasms, Experimental, 77-5521
 Prostatic Neoplasms
 Virus-Like Particles, 77-5852
 Stomach Neoplasms
 Histological Study, 77-5621
 Thyroid Neoplasms
 Hamartoma, 77-5439
 Uterine Neoplasms
 Contraceptives, Oral, 77-5413
 Diagnosis and Prognosis, 77-5910
 Vaginal Neoplasms
 4,4'-Stilbenediol, α,α' -Diethyl-, 77-5445
- Adenofibroma**
 Breast Neoplasms
 Antigens, Viral, 77-5851
- Adenoma**
 Carbamic Acid, Ethyl Ester
 Adhesive Factor, 77-5498
 Lung, Mouse, 77-5498
 Intestinal Neoplasms
 Hydrazine, 1,2-Dimethyl-, 77-5500
 Liver Neoplasms
 Contraceptives, Oral, 77-5523
 Cyprosterone Acetate, 77-5523
 Epidemiology, 77-5525
 Mestranol, 77-5525
 19-Nor-17 α -pregn-4-en-20-yne-3 β ,17-diol, Diacetate
 77-5523
 Norethisterone, 77-5523
 Norethynodrel, 77-5523
 Rat, 77-5523
 Lung Neoplasms
 Benzo(a)pyrene, 77-5550
 Carbamic Acid, Ethyl Ester, 77-5498
 Methane, Tribromo-, 77-5493
 Pyrene, 77-5550
 Water Pollutants, Chemical, 77-5493
 Mammary Neoplasms, Experimental
 Contraceptives, Oral, 77-5527
 Dog, 77-5527
- Adenoma (cont'd)**
 Ethinone, 77-5521, 77-5527
 Histological Study, 77-5527
 Mestranol, 77-5527
 Norgestrel, Chloroethynyl-, 77-5521
 Preg-4-en-20-one, 17-(Acetyloxy)-6 α -methyl-
 77-5521
 Preg-4-en-20-one, 17-Hydroxy-6 α -methyl-, 77-5527
 Prostatic Neoplasms
 Tissue Culture, 77-5915
 Thyroid Neoplasms
 Benzene, Hexachloro-, 77-5483
 Calcium Radioisotopes, 77-5665
 Cesium Radioisotopes, 77-5665
 Strontium Radioisotopes, 77-5665
 Uterine Neoplasms
 Diagnosis and Prognosis, 77-5910
- Adenomyoma**
 see Endometriosis
- Adenosarcoma**
 see Nephroblastoma
- Adenosine Cyclic 3',5' Monophosphate**
 Virus, Kirsten Murine Sarcoma
 Cell Transformation, Neoplastic, 77-5748
 Virus, Moloney Murine Sarcoma
 Neoplasms, Experimental, 77-5746
- Adenosine Deaminase**
 Virus, Rous Sarcoma
 Cell Transformation, Neoplastic, 77-5702
- Adenyl Cyclase**
 Brain
 Enzymatic Activity, 77-5992
 Leukemia, Lymphocytic
 Enzymatic Activity, 77-5997
 Lymphocytes, 77-5997
 Mammary Neoplasms, Experimental
 Mouse, 77-5992
- Adrenal Cortex Hormones**
 Anti-Inflammatory Agents
 Glycoproteins, Review, 77-5451
- Adrenal Gland Neoplasms**
 Asbestos
 Adenocarcinoma, 77-5644
 Hamster, 77-5644
 Carbamic Acid, Methyl-, 1-Naphthyl Ester
 Transplacental Carcinogenesis, Rat, 77-5600
- Aflatoxicol**
 Aflatoxin B1
 Carcinogenic Metabolite, 77-5507
 Hydroxysteroid Dehydrogenases, 77-5507
- Aflatoxin B1**
 Aflatoxicol
 Carcinogenic Metabolite, 77-5507
 Hydroxysteroid Dehydrogenases, 77-5507
 Aroclor 1254
 Carcinogenic Activity, Trout, 77-5506
 Metabolism, Trout, 77-5506
 Averufin
 Mutagenic Activity, Biosynthetic Intermediates
 77-5510
Escherichia coli
 Mutagenic Activity, 77-5511
 Fatty Acids

- Aflatoxin B1 (cont'd)**
 Co-carcinogenic Effect, Fish, 77-5406
 Food Contamination
 Chromatographic Analysis, 77-5513
 Hepatoma
 Aroclor 1254, 77-5506
 Fish, Review, 77-5406
 Liver
 Metabolism, 77-5508
 Mycotoxins
 Histological Study, Duck, Goat, 77-5512
 Norsolorinic Acid
 Mutagenic Activity, Biosynthetic Intermediates
 77-5510
Saccharomyces cerevisiae
 Mutagenic Activity, 77-5511
 Sterigmatocystin
 Mutagenic Activity, Biosynthetic Intermediates
 77-5510
 Versicolorin A
 Mutagenic Activity, Biosynthetic Intermediates
 77-5510
 Versiconal Acetate
 Mutagenic Activity, Biosynthetic Intermediates
 77-5510
- Aflatoxin G1**
Escherichia coli
 Mutagenic Activity, 77-5511
- Aflatoxin M1**
 Food Contamination
 Chromatographic Analysis, 77-5513
- Agglutination**
 Virus, SV40
 Clone Cells, 77-5783
- Aging**
 Cell Transformation, Neoplastic
 Embryo, Mouse, 77-5988
 Cells, Cultured
 Cell Transformation, Neoplastic, 77-5988
 Models, Theoretical, 77-5965
 RNA Replication, 77-5988
 Lead
 Immune Response, 77-5873
 Mouse, 77-5873
 Radiation, Ionizing
 Capillaries, 77-5692
 RNA Replication
 Embryo, Mouse, 77-5988
- Agrobacterium tumefaciens**
 Plant Tumors
 DNA, Bacterial, 77-6000
 Extrachromosomal Inheritance, 77-6000
 Plasmids, 77-6000
- Air Pollution**
 Arsenic
 Epidemiology, Sweden, 77-5947
 Lung Neoplasms
 Arsenic, 77-5947
- Alanine**
 Radiation, Ionizing
 Mutagenic Activity, 77-5649
- Alanine, 3-(3,4-Dihydroxyphenyl)-**
 Melanoma
- Alanine, 3-(3,4-Dihydroxyphenyl)- (cont'd)**
 Virus, Vesicular Stomatitis, 77-5853
- Alcohol Drinking**
 Esophageal Neoplasms
 Epidemiology, 77-5416, 77-5459
 Mouth Neoplasms
 Tobacco, 77-5416
- Aldosterone**
 Mammary Neoplasms, Experimental
 Cell Division, 77-5995
- Alkaline Phosphatase**
 HeLa Cells
 Growth Substances, 77-5994
 Lung Neoplasms
 Enzymatic Activity, 77-5656
- Alpha Particles**
 Cell Transformation, Neoplastic
 Dose-Response Study, 77-5697
- Amino Acids**
 Acetamide, *N*-Fluorenyl-2-yl-
 Metabolism, Rat, 77-5466
 Nafenopin
 Liver, Rat, 77-5531
- Androsta-1,4-dien-3-one, 17 β -Hydroxy-17-methyl-**
 Hepatoma
 Case Report, 77-5921
- 5 α -Androstan-3-one, 17 β -Hydroxy-2 α -methyl-, Propionate**
 Mammary Neoplasms, Experimental
 Benz(a)anthracene, 7,12-Diemthyl-, 77-5577
 Neoplasm Regression, 77-5577
- Anemia, Aplastic**
 Chromosome Aberrations
 Review, 77-5438
 Leukemia
 Statistical Analysis, 77-5440
- Angioma**
see Hemangioma
- Angiosarcoma**
 Arsenic
 Epidemiology, 77-5945
 Ethylene, Chloro-
 Epidemiology, 77-5945
 Liver Neoplasms
 Epidemiology, 77-5944, 77-5945
 Ethylene, Chloro-, 77-5944
 Ethylene, Chloro- Polymer, 77-5944
 Thorium Dioxide
 Epidemiology, 77-5945
- Aniline**
 C.I. Direct Violet 100
 Benzidine, 77-5478
Salmonella typhimurium
 Mutagenic Activity, 77-5479
- Aniline, *N,N*-Dimethyl-*p*-phenylazo-**
 Antigens
 Liver, 77-5482
 Liver Neoplasms
 Immunity, 77-5427
- Anise Oil**
 Liver Regeneration
 Rat, 77-5516

- Anisole, *p*-Allyl-**
Oils
Liver Regeneration, Rat, 77-5516
- Anisole, *p*-Propenyl-**
Oils
Liver Regeneration, Rat, 77-5516
- Anti-Inflammatory Agents**
Adrenal Cortex Hormones
Glycoproteins, Review, 77-5451
- Antibodies, Neoplasm**
Breast Neoplasms
Antigen-Antibody Reactions, 77-5890
Leukocyte Adherence Inhibition, 77-5890
Leukemia, Lymphoblastic
Immune Response, 77-5891
Sarcoma
Mouse, 77-5886
Virus, Baboon C-Type RNA Tumor
Antigens, Viral, 77-5891
Virus, Mason-Pfizer Monkey
Antigens, Viral, 77-5891
Virus, Simian Sarcoma
Antigens, Viral, 77-5891
- Antibodies, Viral**
Burkitt's Lymphoma
Virus, Epstein-Barr, 77-5823
Hodgkin's Disease
Immune Serums, 77-5739
Virus, Gross Murine Leukemia, 77-5739
Leukemia
Immune Serums, 77-5739
Virus, Gross Murine Leukemia, 77-5739
Leukemia, Lymphoblastic
Virus, Gross Murine Leukemia, 77-5739
Leukemia, Myeloblastic
Virus, Gross Murine Leukemia, 77-5739
Lymphoma
Virus, Feline Leukemia, 77-5892
Melanoma
Virus, Baboon, 77-5810
Virus, C-Type RNA Tumor, 77-5810
Virus, Gibbon Ape Leukemia, 77-5810
Virus, Simian Sarcoma, 77-5810
Nasopharyngeal Neoplasms
Carcinoma, 77-5822
Epidemiology, 77-5824, 77-5934
Virus, Epstein-Barr, 77-5823, 77-5824
Pregnancy
Virus, Gross Murine Leukemia, 77-5739
Virus, Bovine Leukemia
Epidemiology, 77-5719, 77-5721
Virus, C-Type RNA Tumor
Virus-Like Particles, A-Type, 77-5770
Virus, Friend Murine Leukemia
Cells, Cultured, 77-5732
Virus, Herpes Simplex 2
Epidemiology, 77-5422
Virus, Papilloma
Immune Response, 77-5847
Virus, Polyoma
Mouse, 77-5759
Pregnancy, Animal, 77-5759
- Antibodies, Viral (cont'd)**
Virus, Rauscher Murine Leukemia
Reverse Transcriptase, 77-5741
- Antibody Formation**
Leukemia, Lymphocytic
Neoplasm Regression, Spontaneous, 77-5731
Multiple Myeloma
Genetics, 77-5875
Sarcoma, Mast Cell
Inhibitory Factor, Culture Supernatant, 77-5861
Virus, Papilloma
IgG, 77-5870
IgM, 77-5870
- Antibody Specificity**
Virus, Leukemia
Virus, Simian Sarcoma, 77-5849
Virus, Mason-Pfizer Monkey
Reverse Transcriptase, 77-5777
- Antigen-Antibody Reactions**
Breast Neoplasms
Antibodies, Neoplasm, 77-5890
Ependymoma
Virus, Papova, BK, 77-5843
Hodgkin's Disease
Antigens, Heterogenetic, 77-5739
Leukemia
Antigens, Heterogenetic, 77-5739
Leukemia, Lymphoblastic
Antigens, Neoplasm, 77-5878
Cell Line, 77-5878
- Antigenic Determinants**
Sarcoma
Teratoid Tumor, 77-5869
Virus, Epstein-Barr
Virus, Herpes Saimiri, 77-5809
Virus, Feline Leukemia
Viral Proteins, 77-5716
Virus, Rauscher Murine Leukemia, 77-5716
Virus, Gazdar Murine Sarcoma
Virus, Moloney Murine Sarcoma, 77-5751
Virus, Mason-Pfizer Monkey
Reverse Transcriptase, 77-5777
Virus, Murine Mammary Tumor
Strain Difference, 77-5757
Viral Proteins, 77-5757
Virus, Radiation Leukemia
Antigens, Viral, 77-5738
Virus, Gross Murine Leukemia, 77-5738
Virus, SV40
DNA, Viral, 77-5790
RNA, Messenger, 77-5790
- Antigens**
Aniline, *N,N*-Dimethyl-*p*-phenylazo-
Liver, 77-5482
Dimethylamine, *N*-Nitroso-
Liver, 77-5482
Liver
Mouse, 77-5482
 α -Toluidine, (4- α -tolylazo)-
Liver, 77-5482
- Antigens, Heterogenetic**
Hodgkin's Disease
Antigen-Antibody Reactions, 77-5739
Leukemia

Antigens, Heterogenetic (cont'd)

- Antigen-Antibody Reactions, 77-5739
- Virus, Friend Murine Leukemia
- Virus Replication, 77-5888

Antigens, Neoplasm

- Breast Neoplasms
 - Carcinoma, 77-5851
 - Leukocyte Adherence Inhibition, 77-5890
- Chondrosarcoma
 - Cells, Cultured, 77-5881
 - Culture Media, 77-5881
- Chromosomes
 - Proteins, 77-5664
- Fibrosarcoma
 - Cells, Cultured, 77-5881
 - Culture Media, 77-5881
 - Isolation and Characterization, 77-5882
- Leukemia, Lymphoblastic
 - Antigen-Antibody Reactions, 77-5878
- Liver Neoplasms
 - Review, 77-5427
- Lymphosarcoma
 - Virus, Bovine Leukemia, 77-5883
- Sarcoma
 - Immune Response, 77-5854
- Sarcoma, Osteogenic
 - Isolation and Characterization, 77-5882
 - Radiation, Ionizing, 77-5664
- Virus, Marek's Disease Herpes
 - Immunity, Cellular, 77-5880
- Virus, SV40
 - Hamster, 77-5794

Antigens, Viral

- Breast Neoplasms
 - Adenofibroma, 77-5851
 - Carcinoma, 77-5756
 - Virus, D-Type RNA Tumor, 77-5851
 - Virus, Murine Mammary Tumor, 77-5756
- Burkitt's Lymphoma
 - Cells, Cultured, 77-5828
 - Virus, Adeno 5, 77-5828
- Estradiol
 - Virus, Murine Mammary Tumor, 77-5753
- B-Lymphocytes
 - Virus, C-Type RNA Tumor, 77-5769
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Virus, Murine Mammary Tumor, 77-5753
- Virus, Adeno
 - Cells, Cultured, 77-5724
 - Immune Response, 77-5724
- Virus, Adeno 2 - SV40 Hybrid
 - HeLa Cells, 77-5802
- Virus, Avian Sarcoma
 - Cell Transformation, Neoplastic, 77-5710
- Virus, Baboon C-Type RNA Tumor
 - Antibodies, Neoplasm, 77-5891
- Virus, D-Type RNA Tumor
 - Cells, Cultured, 77-5851
- Virus, Epstein-Barr
 - Arginine, 77-5821
 - Cells, Cultured, 77-5820, 77-5822
 - DNA Replication, 77-5821
 - Plant Agglutinins, 77-5821
- Virus, Feline Leukemia
 - Cell Membrane, 77-5717
 - Epidemiology, 77-5718

Antigens, Viral (cont'd)

- Virus, Friend Murine Leukemia
 - Cell Transformation, Neoplastic, 77-5767
- Virus, Gross Murine Leukemia
 - Cell Membrane, 77-5738
- Virus, Mason-Pfizer Monkey
 - Antibodies, Neoplasm, 77-5891
- Virus, Moloney Murine Leukemia
 - Virus, Moloney Murine Sarcoma, 77-5745
- Virus, Papova
 - Isolation and Characterization, 77-5807
- Virus, Papova, BK
 - Isolation and Characterization, 77-5806, 77-5807
- Virus, Papova, JC
 - Isolation and Characterization, 77-5807
- Virus, Parvo
 - Cellular Inclusions, 77-5798
 - Chromatin, 77-5798
 - Temperature Sensitive Mutants, H-1 Virus, 77-5798
 - Ultrastructural Study, 77-5798
- Virus, Polyoma, BK
 - Urine, 77-5842
- Virus, Polyoma, JC
 - Urine, 77-5842
- Virus, Radiation Leukemia
 - Antigenic Determinants, 77-5738
 - Cell Membrane, 77-5738
 - Macrophages, 77-5871
 - Virus, Gross Murine Leukemia, 77-5738
- Virus, Rous Sarcoma
 - Cell Transformation, Neoplastic, 77-5708, 77-5711
- Virus, Sendai
 - Cells, Cultured, 77-5820
- Virus, Simian Sarcoma
 - Antibodies, Neoplasm, 77-5891
- Virus, SV40
 - Binding, 77-5801
 - Chromatin, 77-5801
 - DNA, 77-5801
 - HeLa Cells, 77-5802
 - Isolation and Characterization, 77-5807
 - Mouse, 77-5884
 - Virus, Papova, BK, 77-5806
 - Virus Replication, 77-5785

Antineoplastic Agents

- Multiple Myeloma
 - Cell Survival, 77-5962

Antioxidants

- Ultraviolet Rays
 - Carcinogenic Activity, Review, 77-5421

Antipyrene

- Liver
 - Hydroxylases, 77-5569
 - Metabolism, 77-5569

Arginine

- Nitrous Acid, Sodium Salt
 - Carcinogenic Potential, Rat, 77-5602
- Virus, Epstein-Barr
 - Antigens, Viral, 77-5821

Aroclor 1254

- Aflatoxin B1
 - Carcinogenic Activity, Trout, 77-5506
 - Metabolism, Trout, 77-5506
- Hepatoma
 - Aflatoxin B1, 77-5506

Aroclor 1254 (cont'd)

- Kidney
 - Metabolism, Trout, 77-5506
- Liver Neoplasms
 - Metabolism, Trout, 77-5506

Arsenic

- Air Pollution
 - Epidemiology, Sweden, 77-5947
- Angiosarcoma
 - Epidemiology, 77-5945
- Arsinic Acid, Dimethyl-
 - Excretion, Urine, 77-5641
- Gangrene
 - Epidemiology, Taiwan, 77-5638
- Liver Neoplasms
 - Hemangioendothelioma, 77-5637
- Lung Neoplasms
 - Air Pollution, 77-5947
 - Epidemiology, Sweden, 77-5947
 - Occupational Hazard, 77-5947
- Lymphocytes
 - Cell Division, 77-5640
 - Chromosome Aberrations, 77-5639, 77-5640
 - DNA Replication, 77-5640
- Methanearsonic Acid
 - Excretion, Urine, 77-5641
- Occupational Hazard
 - Chromosome Aberrations, 77-5639
 - Trace Elements, Review, 77-5412
- Skin Neoplasms
 - Carcinoma, 77-5637
 - Chromosome Aberrations, 77-5640
 - Epidemiology, Taiwan, 77-5638
 - Water Pollution, 77-5638
- Vascular Diseases
 - Epidemiology, Taiwan, 77-5638
- Water Pollution
 - Epidemiology, 77-5637
 - Epidemiology, Taiwan, 77-5638

Arsenic Acid

- Arsinic Acid, Dimethyl-
 - Excretion, Urine, 77-5641
- Methanearsonic Acid
 - Excretion, Urine, 77-5641

Arsenic Acid, Sodium Salt

- Mitochondria, Liver
 - Cytochrome Oxidase, 77-5642
 - Malate Dehydrogenase, 77-5642
 - Mitochondrial Swelling, 77-5642
 - Monoamine Oxidase, 77-5642
 - Pyruvate Dehydrogenase Complex, 77-5643
 - Ultrastructural Study, Rat, 77-5642
- Respiratory Function
 - Mitochondrial Swelling, 77-5642
- Ultrastructural Study, Rat
 - Mitochondrial Swelling, 77-5642

Arsenic Trioxide

- Arsinic Acid, Dimethyl-
 - Excretion, Urine, 77-5641
- Digestive System Neoplasms
 - Occupational Hazard, 77-5636
- Methanearsonic Acid
 - Excretion, Urine, 77-5641
- Occupational Hazard
 - Epidemiology, 77-5636

Arsenic Trioxide (cont'd)

- Respiratory Tract Neoplasms
 - Occupational Hazard, 77-5636

Arsinic Acid, Dimethyl-

- Arsenic
 - Excretion, Urine, 77-5641
- Arsenic Acid
 - Excretion, Urine, 77-5641
- Arsenic Trioxide
 - Excretion, Urine, 77-5641

Aryl Hydrocarbon Hydroxylases

- Benz(a)anthracene, 7,12-Dimethyl-
 - Metabolism, 77-5570
- Benzo(a)pyrene
 - Isolation and Characterization, 77-5553
 - Metabolism, 77-5570
 - NADPH, 77-5544
 - Uridine Diphosphate Sugars, 77-5564
- Benzo(b)triphenylene
 - NADPH, 77-5544
- 5,6-Benzoflavone
 - Enzymatic Activity, 77-5548
- 7,8-Benzoflavone
 - Enzymatic Activity, 77-5548
- Cells, Cultured
 - Enzymatic Activity, 77-5588
- Cholanthrene, 3-Methyl-
 - Genetics, Mouse, 77-5592
 - Liver, Lung, Mouse, 77-5592
 - Lymphocytes, 77-5588
 - NADPH, 77-5544
- Concanavalin A
 - Lymphocytes, 77-5588
- Dibenz(a,h)anthracene
 - NADPH, 77-5544
- DNA
 - Binding, 77-5544
- Kidney Neoplasms
 - Carcinoma, 77-5589
 - Smoking, 77-5589
- Lung
 - Enzymatic Activity, 77-5590
- Lymphocytes
 - Enzymatic Activity, 77-5588, 77-5590, 77-5591
 - Smoking, 77-5591
- Macrophages
 - Enzymatic Activity, 77-5590, 77-5591
 - Smoking, 77-5591
- Mitogens
 - Lymphocytes, 77-5588
- Plant Agglutinins
 - Lymphocytes, 77-5588
- Smoking
 - Genetics, Mouse, 77-5592
 - Liver, Lung, Mouse, 77-5592
- Ureteral Neoplasms
 - Carcinoma, 77-5589
 - Smoking, 77-5589

Asbestos

- Adrenal Gland Neoplasms
 - Adenocarcinoma, 77-5644
 - Hamster, 77-5644
- Cells, Cultured
 - Histological Study, 77-5646
- Fibrosarcoma
 - Rat, 77-5644

Asbestos (cont'd)

- Intestinal Neoplasms
 - Epidemiology, 77-5955
- Kidney Neoplasms
 - Epidemiology, 77-5955
- Lung
 - Chemical Analysis, Fibers, 77-5647
 - Histological Study, 77-5953
 - Phagocytosis, 77-5647
- Lung Neoplasms
 - Case Report, 77-5954
 - Mesothelioma, 77-5952, 77-5954
- Melanoma
 - Epidemiology, 77-5955
- Mesothelioma
 - Epidemiology, 77-5417
- Mouth Neoplasms
 - Epidemiology, 77-5955
- Occupational Hazard
 - Phagocytosis, 77-5647
- Peritoneal Neoplasms
 - Epidemiology, 77-5955
- Pheochromocytoma
 - Hamster, 77-5644
- Pleural Neoplasms
 - Diagnosis and Prognosis, 77-5645
 - Epidemiology, 77-5645, 77-5955
 - Mesothelioma, 77-5645
- Salivary Gland Neoplasms
 - Epidemiology, 77-5955
- Toxicology
 - Cells, Cultured, 77-5410
- Water Pollution
 - Lung Neoplasms, 77-5957
 - Pancreatic Neoplasms, 77-5957
 - Stomach Neoplasms, 77-5957

Asbestosis

- Lung Neoplasms
 - Epidemiology, 77-5954

Ascorbic Acid

- Breast Neoplasms
 - Collagen, 77-5983
- Kidney Neoplasms
 - Dimethylamine, *N*-Nitroso-, 77-5599
- Liver Neoplasms
 - Dimethylamine, *N*-Nitroso-, 77-5599
- Lung Neoplasms
 - Dimethylamine, *N*-Nitroso-, 77-5599

Ascorbic Acid, Monosodium Salt

- Dimethylamine, *N*-Nitroso-
Rat, 77-5610

Aspergillus nidulans

- Radiation, Ionizing
 - Mutagenic Activity, 77-5651

Aspergillus parasiticus

- Versiconal Hemiacetal Acetate
 - Biosynthesis, 77-5509

Astrocytoma

- Brain Neoplasms
 - Case Report, 77-5901
 - Genetics, 77-5901
 - Histological Study, 77-5901

Ataxia Telangiectasia

- Chromosome Aberrations

Ataxia Telangiectasia (cont'd)

- Review, 77-5438
- Leukemia
 - Immunologic Deficiency Syndromes, 77-5434
- Lymphoma
 - Epidemiology, 77-5444
 - Immunologic Deficiency Syndromes, 77-5434
- Neoplasms
 - Statistical Analysis, 77-5440
- Radiation, Ionizing
 - DNA Repair, 77-5433
- Stomach Neoplasms
 - Carcinoma, 77-5440

Averufin

- Aflatoxin B1
 - Mutagenic Activity, Biosynthetic Intermediates
77-5510

Azathioprine

- Mammary Neoplasms, Experimental
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-5579

Bactopeptone

- Growth Substances
 - Cells, Cultured, 77-5966

Barbituric Acid, 5-(1-Cyclohexen-1-yl)-1,5-dimethyl-

- Liver
 - Hydroxylases, 77-5569
 - Metabolism, 77-5569

Benz(a)anthracene

- Coliphages
 - DNA, 77-5545
 - RNA, 77-5545
- Deuterium
 - Synthesis, 77-5567
- Fish
 - Tissue Concentrations, 77-5549

Benz(a)anthracene, 7-Bromomethyl-

- DNA
 - Binding, 77-5582
- DNA Repair
 - Cells, Cultured, 77-5581
- DNA Replication, 77-5582

Benz(a)anthracene, 5,6-Dihydro-5,6-epoxy-

- Coliphages
 - DNA, 77-5545
 - RNA, 77-5545
- Liver
 - Hydro-Lyases, 77-5543

Benz(a)anthracene, 7,12-Dimethyl-

- Aryl Hydrocarbon Hydroxylases
 - Metabolism, 77-5570
- Cell Transformation, Neoplastic
 - Karyotyping, 77-5630
- Cells, Cultured
 - Metabolism, 77-5570
- Coliphages
 - DNA, 77-5545
 - RNA, 77-5545
- DNA
 - Binding, 77-5544, 77-5548, 77-5570, 77-5576
- Leukemia
 - Virus, C-Type RNA Tumor, 77-5765
 - Virus Replication, 77-5765
- Leukemia, Myeloblastic

- Benz(a)anthracene, 7,12-Dimethyl- (cont'd)**
 Chromosomes, 77-5575
 Cytochemical Study, 77-5575
 DNA, 77-5575
 Ultrastructural Study, 77-5575
 Mammary Neoplasms, Experimental
 5 α -Androstan-3-one, 17 β -Hydroxy-2 α -methyl-,
 Propionate, 77-5577
 Azathioprine, 77-5579
Corynebacterium parvum, 77-5579
 Ergolines, 77-5577
 Ergot Alkaloids, 77-5577
 Estradiol, 77-5577
 Hormones, 77-5996
 Metabolism, Liver, 77-5574
 Rat, 77-5578
 Mouth Neoplasms
 Carcinoma, 77-5571
 Cell-Cycle Kinetics, 77-5572
 Proteins
 Liver, Rat, 77-5574
 RNA, Transfer, Methyltransferases
 Liver, Rat, 77-5574
 Sarcoma
 Glucosaminidase, 77-5573
 Lysosomes, 77-5573
 Skin Neoplasms
 5,6-Benzoflavone, 77-5548
 7,8-Benzoflavone, 77-5548
- Benz(a)anthracene, 7-Methyl-**
 Cell Transformation, Neoplastic
 Carcinogenic Metabolite, 77-5580
 Cells, Cultured
 Mutagenic Activity, 77-5580
- Benz(a)anthracene, 12-Methyl-7-oxiranyl-**
 Coliphages
 DNA, 77-5545
 RNA, 77-5545
- Benzaldehyde, *p*-Isopropyl-**
 Oils
 Liver Regeneration, Rat, 77-5516
- Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-**
 Hepatoma
 Lecithins, 77-5481
 Liver Neoplasms
 Selenium, 77-5480
- Benzene**
 Cell Nucleus
 RNA, 77-5551
 Soot
 Carcinogenic Activity, Mouse, 77-5552
- Benzene, 4-Allyl-1,2-(methylenedioxy)-**
 Oils
 Liver Regeneration, Rat, 77-5516
- Benzene, (Epoxyethyl)-**
 Epoxide Hydratases
 Enzymatic Activity, 77-5542
- Benzene, Hexachloro-**
 Carcinogenic Activity
 Hamster, 77-5483
 Hemangioendothelioma
 Hamster, 77-5483
 Hepatoma
- Benzene, Hexachloro- (cont'd)**
 Hamster, 77-5483
 Liver Neoplasms
 Hemangioendothelioma, 77-5483
 Splenic Neoplasms
 Hemangioendothelioma, 77-5483
 Thyroid Neoplasms
 Adenoma, 77-5483
- Benzene, 1,2-(Methylenedioxy)-4-propenyl-**
 Oils
 Liver Regeneration, Rat, 77-5516
- Benzidine**
 C.I. Direct Violet 100
 Aniline, 77-5478
- Benzo(a)pyrene**
 Aryl Hydrocarbon Hydroxylases
 Isolation and Characterization, 77-5553
 Metabolism, 77-5570
 NADPH, 77-5544
 Cell Nucleus
 RNA, 77-5551
 Cell Transformation, Neoplastic
 Carcinogenic Metabolite, 77-5562
 Cell-Cycle Kinetics, 77-5968
 Karyotyping, 77-5630
 Virus, Hamster C-Type RNA Tumor, 77-5773
 Cells, Cultured
 Chromosome Aberrations, 77-5631
 Metabolism, 77-5559, 77-5570
 Cholanthrene, 3-Methyl-
 Metabolism, 77-5566
 Coliphages
 DNA, 77-5545
 RNA, 77-5545
 Cytochrome P-448
 Metabolism, 77-5554
 Deuterium
 Synthesis, 77-5567
 DNA
 Binding, 77-5544, 77-5557, 77-5565, 77-5568
 77-5570
 RNA, 77-5557
 DNA Repair
 Cells, Cultured, 77-5673
 Fibrinolysis
 Cell Transformation, Neoplastic, 77-5556
 Cells, Cultured, 77-5556
 Fish
 Tissue Concentrations, 77-5549
 Growth Substances
 Cell-Cycle Kinetics, 77-5968
 Phosphoinositides, 77-5968
 Hydroxylation
 Microsomes, Liver, 77-5555
 Liver
 Hydroxylases, 77-5569
 Metabolism, 77-5566, 77-5569
 Liver Neoplasms
 Cells, Cultured, 77-5559
 Metabolism, 77-5559
 Transplacental Carcinogenesis, 77-5550
 Lung
 Metabolism, 77-5566
 Lung Neoplasms
 Adenoma, 77-5550
Mycobacterium bovis, 77-5868
 Lymphocytes

- Benzo(a)pyrene (cont'd)**
 Cell-Cycle Kinetics, 77-5627
 Chromosome Aberrations, 77-5627
 Mammary Neoplasms, Experimental
 Transplacental Carcinogenesis, 77-5550
 Metabolism
 Binding, 77-5565
 Monkey, 77-5566
 Rat, 77-5566
 Microsomes, Liver
 Cytochrome P-450, 77-5555
 Cytochromes, 77-5555
 NADPH Cytochrome C Reductase, 77-5555
 Phosphoinositides
 Cell Transformation, Neoplastic, 77-5968
 Plants
 Metabolism, 77-5558
 Proteins
 Binding, 77-5565
 RNA
 Binding, 77-5557, 77-5565, 77-5568
 Skin Neoplasms
 Mouse, 77-5560
 Soot
 Carcinogenic Activity, Mouse, 77-5552
 Transplacental Carcinogenesis
 Mouse, 77-5550
 Uridine Diphosphate Sugars
 Aryl Hydrocarbon Hydroxylases, 77-5564
 Metabolism, Liver, 77-5564
 Oxidoreductases, 77-5564
- Benzo(a)pyrene, 4,5-Dihydro-4,5-dihydroxy-**
 Glucuronidase
 Metabolism, Hamster, 77-5563
 Lung
 Metabolism, Hamster, 77-5563
 Trachea
 Metabolism, Hamster, 77-5563
- Benzo(a)pyrene, (+)-trans-7,8-Dihydroxy-7,8-dihydro-**
 Skin Neoplasms
 Mouse, 77-5561
- Benzo(a)pyrene 4,5-Oxide**
 Epoxide Hydratases
 Enzymatic Activity, 77-5542
 Liver
 Hydro-Lyases, 77-5543
- Benzo(a)pyrene 7,8-Oxide**
 Liver
 Hydro-Lyases, 77-5543
- Benzo(a)pyrene 11,12-Oxide**
 Liver
 Hydro-Lyases, 77-5543
- Benzo(a)pyren-2-ol**
 Skin Neoplasms
 Mouse, 77-5560
- Benzo(a)pyren-11-ol**
 Skin Neoplasms
 Mouse, 77-5560
- Benzo(b)triphenylene**
 Aryl Hydrocarbon Hydroxylases
 NADPH, 77-5544
 DNA
- Benzo(b)triphenylene (cont'd)**
 Binding, 77-5544
- 5,6-Benzoflavone**
 Aryl Hydrocarbon Hydroxylases
 Enzymatic Activity, 77-5548
 Skin Neoplasms
 Benz(a)anthracene, 7,12-Dimethyl-, 77-5548
 Cholanthrene, 3-Methyl-, 77-5548
 Dibenz(a,h)anthracene, 77-5548
- 7,8-Benzoflavone**
 Aryl Hydrocarbon Hydroxylases
 Enzymatic Activity, 77-5548
 Skin Neoplasms
 Benz(a)anthracene, 7,12-Dimethyl-, 77-5548
 Cholanthrene, 3-Methyl-, 77-5548
 Dibenz(a,h)anthracene, 77-5548
- Benzoic Acid, 2-(Acetyloxy)-**
 Gastric Mucosa
 Glycoproteins, Review, 77-5451
- Benzylamine**
 Dimethylamine, *N*-Nitroso-
 Metabolism, 77-5609
- Beryllium**
 DNA Replication
 Carcinogenic Activity, 77-5634
 Mutagenic Activity, 77-5634
 Neoplasms, Experimental
 Trace Elements, Review, 77-5412
- Biphenyl**
 Ethane, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)-
 Hydroxylation, Microsomes, Liver, 77-5485
 Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-
 Hydroxylation, Microsomes, Liver, 77-5485
 Ethylene, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)-
 Hydroxylation, Microsomes, Liver, 77-5485
- Biphenyl, 2,2',4,4',5,5'-Hexabromo-**
 Liver Neoplasms
 Rat, 77-5486
- Biphenyl, 4-Nitro-**
Salmonella typhimurium
 Gastrointestinal System, Rat, 77-5473
 Revertants, Germ-Free Rat, 77-5473
- 4-Biphenylamine, 3,2'-Dimethyl-**
Salmonella typhimurium
 Gastrointestinal System, Rat, 77-5473
 Revertants, Germ-Free Rat, 77-5473
- Bladder**
 Cells, Cultured
 Histological Study, 77-5976
 Putrescine, 77-5976
 Rat, 77-5976
 Spermidine, 77-5976
 Spermine, 77-5976
 Hyperplasia
 F12 Medium, 77-5977
 Organ Culture, 77-5977
- Bladder Neoplasms**
 1-Butanol, 4-(Butylnitrosamino)-
 Leupeptins, 77-5606
 Oligopeptides, 77-5606
 Carcinoma
 1-Butanol, 4-(Butylnitrosamino)-, 77-5978

- Bladder Neoplasms (cont'd)**
 - Butyric Acid, 4-Butylamino-*N*-nitroso-, 77-5978
 - Carcinoembryonic Antigen, 77-5889
 - Ultrastructural Study, 77-5464, 77-5978
 - Urea, 77-5978
 - Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-Rat, 77-5464
 - Ultrastructural Study, 77-5464
 - Glycoproteins
 - Isolation and Characterization, 77-5889
 - Leupeptins
 - Ultrastructural Study, Rat, 77-5606
 - Microsomes, Liver
 - Carcinogenic Metabolite, 77-5472
 - Glucuronidase, 77-5472
 - Occupational Hazard
 - Epidemiology, 77-5417
 - Oligopeptides
 - Cell Transformation, Neoplastic, 77-5606
 - Smoking
 - Epidemiology, 77-5416
- Blood Proteins**
 - Liver Regeneration
 - Isolation and Characterization, 77-5982
 - Multiple Myeloma
 - Genetics, 77-5875
 - Rhabdomyosarcoma
 - Immune Response, 77-5863
- Bone and Bones**
 - Plutonium
 - Dog, 77-5662
 - Histological Study, Hamster, Rabbit, 77-5659
- Bone Marrow Cells**
 - Leukemia
 - Reverse Transcriptase, 77-5849
 - Virus, Leukemia, 77-5849
 - Leukemia, Lymphocytic
 - Virus, Murine Leukemia, 77-5740
- Bone Neoplasms**
 - Ethnic Groups
 - Epidemiology, 77-5458
- Brain**
 - Adenyl Cyclase
 - Enzymatic Activity, 77-5992
- Brain Neoplasms**
 - Astrocytoma
 - Case Report, 77-5901
 - Genetics, 77-5901
 - Histological Study, 77-5901
 - Breast Neoplasms
 - Genetics, 77-5442
 - Glioblastoma Multiforme
 - Guanyl Cyclase, 77-5993
 - Glioma
 - Urea, Ethyl Nitroso-, 77-5613
 - Guanyl Cyclase
 - Enzymatic Activity, 77-5993
 - Meningioma
 - Guanyl Cyclase, 77-5993
 - Neurinoma
 - Guanyl Cyclase, 77-5993
 - Oligodendroglioma
 - Guanyl Cyclase, 77-5993
 - Sarcoma
- Brain Neoplasms (cont'd)**
 - Genetics, 77-5442
- Breast Neoplasms**
 - Adenofibroma
 - Antigens, Viral, 77-5851
 - Antibodies, Neoplasm
 - Antigen-Antibody Reactions, 77-5890
 - Leukocyte Adherence Inhibition, 77-5890
 - Antigens, Neoplasm
 - Leukocyte Adherence Inhibition, 77-5890
 - Ascorbic Acid
 - Collagen, 77-5983
 - Blood Groups
 - Epidemiology, Great Britain, 77-5933
 - Brain Neoplasms
 - Genetics, 77-5442
 - Carcinoma
 - Antigens, Neoplasm, 77-5851
 - Antigens, Viral, 77-5756
 - Epidemiology, 77-5931
 - Hamartoma, 77-5439
 - Histological Study, 77-5930
 - Neoplasm Metastasis, 77-5930
 - Receptors, Hormone, 77-5918
 - Spectrum Analysis, 77-5850
 - Virus, Murine Sarcoma, 77-5850
 - Cell Division
 - Protons, 77-5960
 - Cells, Cultured
 - Cell Division, 77-5960
 - Collagen, 77-5983
 - Models, Biological, 77-5576
 - Nuclear Magnetic Resonance Properties, 77-5960
 - Collagen
 - Isolation and Characterization, 77-5983
 - Colonic Neoplasms
 - Epidemiology, US, 77-5932
 - Culture Media
 - Cell Division, 77-5971
 - Endocrinology
 - Genetics, 77-5454
 - Epidemiology
 - Models, Theoretical, 77-5455
 - Estradiol
 - Cell Survival, 77-5996
 - Estrogens
 - Food Contamination, 77-5414
 - Ethnic Groups
 - Epidemiology, US, 77-5932
 - Ethylene, Chloro- Polymer
 - Epidemiology, 77-5946
 - Fatty Acids
 - Risk Factor, Review, 77-5461
 - Food Contamination
 - Mycotoxins, 77-5414
 - Genetics
 - Case Report, 77-5689
 - Epidemiology, 77-5443
 - Growth Substances
 - Cell Division, 77-5971
 - Neoplasms
 - Genetics, 77-5442
 - Neoplasms, Multiple Primary
 - Genetics, 77-5442
 - Nephroblastoma
 - Radiotherapy, 77-5689
 - Occupational Hazard

- Breast Neoplasms (cont'd)**
 Epidemiology, 77-5946, 77-5951
- Ovarian Neoplasms**
 Epidemiology, US, 77-5932
- Parity**
 Epidemiology, US, 77-5932
- Precancerous Conditions**
 Diagnosis and Prognosis, 77-5929
 Epidemiology, 77-5929
- Prolactin**
 Cell Survival, 77-5996
- Propionitrile, 3-Amino-**
 Collagen, 77-5983
- Radiation, Ionizing**
 Case Report, 77-5689
 Epidemiology, 77-5457, 77-5694
- Rauwolfia**
 Epidemiology, 77-5529
- Socioeconomic Factors**
 Epidemiology, US, 77-5932
- Testosterone**
 Cell Survival, 77-5996
- Virus, D-Type RNA Tumor**
 Antigens, Viral, 77-5851
- Virus, Murine Mammary Tumor**
 Antigens, Viral, 77-5756
- Bromocriptine**
 Uterine Neoplasms
 Epidemiology, 77-5530
- Bronchi**
 Diethylamine, *N*-Nitroso-
 DNA, Binding, 77-5603
 Metabolism, 77-5603
- Dimethylamine, N-Nitroso-**
 DNA, Binding, 77-5603
 Metabolism, 77-5603
- Lung Neoplasms**
 Nitrosamines, 77-5603
- Piperazine, 1,4-Dinitroso-**
 DNA, Binding, 77-5603
 Metabolism, 77-5603
- Pyrrolidine, 1-Nitroso-**
 DNA, Binding, 77-5603
 Metabolism, 77-5603
- Bronchial Neoplasms**
 Blood Groups
 Epidemiology, Great Britain, 77-5933
- Burkitt's Lymphoma**
 Cells, Cultured
 Antigens, Viral, 77-5828
- Virus, Adeno 5**
 Antigens, Viral, 77-5828
 Virus Replication, 77-5827
- Virus, Epstein-Barr**
 Antibodies, Viral, 77-5823
 DNA, Viral, 77-5826
 Epidemiology, 77-5457, 77-5825
 Review, 77-5446
 Viral Proteins, 77-5828
- 1,3-Butadiene, 2-Chloro-**
 Carcinogenic Potential
 Mouse, 77-5597
- 1-Butanamine, N-Butyl-N-nitroso-**
 Nitrous Acid
- 1-Butanamine, N-Butyl-N-nitroso- (cont'd)**
Saccharomycopsis lipolytica, 77-5604
- Butane, 1,2-Epoxy-**
Salmonella typhimurium
 Mutagenic Activity, 77-5488
- 1-Butanol, 2-Amino-**
 Lipids
 Cell Membrane, 77-5706
- 1-Butanol, 4-(Butylnitrosamino)-**
 Bladder Neoplasms
 Carcinoma, 77-5978
 Leupeptins, 77-5606
 Oligopeptides, 77-5606
- Butyric Acid, 2-Amino-4-(ethylthio)-**
 Hepatoma
 Choline, Chloride, Carbamate, 77-5499
 Guanosine Cyclic 3',5' Monophosphate, 77-5499
 Guanyl Cyclase, 77-5499
 Phosphodiesterases, 77-5499
 Xanthine, 3-Isobutyl-1-methyl-, 77-5499
- Butyric Acid, 4-Butylamino-N-nitroso-**
 Bladder Neoplasms
 Carcinoma, 77-5978
- C.I. Acid Violet 49, Sodium Salt**
 Rat
 Metabolism, 77-5477
- C.I. Direct Violet 100**
 Aniline
 Benzidine, 77-5478
- Cholangioma**
 Rat, 77-5478
- Leukemia**
 Rat, 77-5478
- Plasmacytoma**
 Rat, 77-5478
- Cadmium**
 DNA Replication
 Carcinogenic Activity, 77-5634
 Mutagenic Activity, 77-5634
 Neoplasms, Experimental
 Trace Elements, Review, 77-5412
- Caffeine**
 Cells, Cultured
 Chromosome Aberrations, 77-5631
- Chromosome Aberrations**
 Cells, Cultured, 77-5629
- DNA Repair, 77-5582**
 Mutagenic Activity, 77-5679
- Ultraviolet Rays**
 Mutagenic Activity, 77-5679
- Calcium Radioisotopes**
 Thyroid Neoplasms
 Adenoma, 77-5665
 Carcinoma, 77-5665
- Candidin**
 Intestinal Neoplasms
 Methane, Azoxy-, 77-5474
- Capillaries**
 Aging

- Capillaries (cont'd)
 - Radiation, Ionizing, 77-5692
- Carbamic Acid, Ethyl Ester
 - Adenoma
 - Adhesive Factor, 77-5498
 - Lung, Mouse, 77-5498
 - Lung Neoplasms
 - Adenoma, 77-5498
 - Mammary Neoplasms, Experimental
 - Adenocarcinoma, 77-5497
 - Neoplasm Transplantation
 - Mouse, 77-5497
- Carbamic Acid, Methyl-, 1-Naphthyl Ester
 - Adrenal Gland Neoplasms
 - Transplacental Carcinogenesis, Rat, 77-5600
 - Mammary Neoplasms, Experimental
 - Transplacental Carcinogenesis, Rat, 77-5600
 - Nitrous Acid, Sodium Salt
 - Transplacental Carcinogenesis, Rat, 77-5600
 - Pituitary Neoplasms
 - Transplacental Carcinogenesis, Rat, 77-5600
- Carbamic Acid, Nitro-, Ethyl Ester
 - Pancreatic Neoplasms
 - Epidemiology, Review, 77-5449
- Carbazole
 - Deuterium
 - Synthesis, 77-5567
- Carbenoxolone
 - Carbohydrates
 - Mucosal Glycoproteins, Review, 77-5452
 - Carcinogen, Chemical
 - Mucosal Glycoproteins, Review, 77-5452
 - Cervix Uteri
 - Mucosal Glycoproteins, Review, 77-5452
 - Endometrium
 - Mucosal Glycoproteins, Review, 77-5452
 - Gastrointestinal System
 - Cervix Uteri, 77-5452
 - Respiratory System
 - Mucosal Glycoproteins, Review, 77-5452
- Carbohydrates
 - Carbenoxolone
 - Mucosal Glycoproteins, Review, 77-5452
 - Colonic Neoplasms
 - Glycoproteins, Review, 77-5450
- Carbon Tetrachloride
 - Liver
 - Histological Study, Rat, 77-5547
 - Ultrastructural Study, Rat, 77-5547
 - Neoplasms
 - Fish, 77-5958
 - Polycyclic Hydrocarbons
 - Free Radicals, 77-5547
 - Succinate Dehydrogenase
 - Enzymatic Activity, 77-5546
- Carboxy-Lyases
 - Nafenopin
 - Liver, Rat, 77-5531
- Carcinoembryonic Antigen
 - Bladder Neoplasms
 - Carcinoma, 77-5889
 - Choriocarcinoma
 - Cells, Cultured, 77-5970
- Carcinoembryonic Antigen (cont'd)
 - Colonic Neoplasms
 - Adenocarcinoma, 77-5970
 - Carcinoma, 77-5889
 - Cells, Cultured, 77-5970
 - Sarcoma
 - Cholanthrene, 3-Methyl-, 77-5869
 - Immunologic Technics, 77-5869
- Carcinogen, Chemical
 - Animals, Laboratory
 - Dose-Response Study, 77-5409
 - Carbenoxolone
 - Mucosal Glycoproteins, Review, 77-5452
 - DNA
 - Carcinogenesis Model, Review, 77-5432
 - Endoplasmic Reticulum
 - Mucosal Glycoproteins, Review, 77-5452
 - Environmental Hazard
 - Risk Factor, Statistical Analysis, 77-5409
 - Occupational Hazard
 - Legislation, 77-5949
 - Water Pollution
 - Concentration Levels, Review, 77-5402
- Carcinogen, Environmental
 - Aquatic Animals
 - Epidemiology, Review, 77-5404
 - Cell Transformation, Neoplastic
 - Animal Model, Fish, Review, 77-5405
 - DNA Repair
 - Carcinogenic Activity, Review, 77-5411
 - Mutagenic Activity, Review, 77-5411
 - Quantitation Method, Review, 77-5411
 - Esophageal Neoplasms
 - Epidemiology, 77-5459
 - Fish
 - Epidemiology, Review, 77-5404
 - Mammary Neoplasms, Experimental
 - Mouse, 77-5648
 - Mouth Neoplasms
 - Epidemiology, 77-5459
 - Occupational Hazard
 - Epidemiology, 77-5417
 - Pharyngeal Neoplasms
 - Epidemiology, 77-5459
- Carcinoid Tumor
 - Genetics
 - Review, 77-5447
 - Ovarian Neoplasms
 - Case Report, 77-5917
 - Histological Study, 77-5917
 - Ultrastructural Study, 77-5917
- Carcinoma
 - Bladder Neoplasms
 - 1-Butanol, 4-(Butylnitrosamino)-, 77-5978
 - Butyric Acid, 4-Butylamino-*N*-nitroso-, 77-5978
 - Carcinoembryonic Antigen, 77-5889
 - Ultrastructural Study, 77-5464, 77-5978
 - Urea, 77-5978
 - Breast Neoplasms
 - Antigens, Neoplasm, 77-5851
 - Antigens, Viral, 77-5756
 - Epidemiology, 77-5931
 - Hamartoma, 77-5439
 - Histological Study, 77-5930
 - Neoplasm Metastasis, 77-5930

Carcinoma (cont'd)

- Receptors, Hormone, 77-5918
- Spectrum Analysis, 77-5850
- Virus, Murine Sarcoma, 77-5850
- Cervix Neoplasms
 - Virus, Herpes Simplex 2, 77-5422
- Colonic Neoplasms
 - Carcinoembryonic Antigen, 77-5889
 - Hydrazine, 1,2-Dimethyl-, Dihydrochloride, 77-5501
 - Methane, 77-5476
- Intestinal Neoplasms
 - Hydrazine, 1,2-Dimethyl-, 77-5500
- Kidney Neoplasms
 - Aryl Hydrocarbon Hydroxylases, 77-5589
 - Case Report, 77-5690
 - Radiation, Ionizing, 77-5690
- Liver Neoplasms
 - Epidemiology, 77-5525
 - Megestrol Acetate, 77-5523
 - Mestranol, 77-5525
 - Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester) 77-5475
 - Norethynodrel, 77-5523
 - Rat, 77-5523
- Lung Neoplasms
 - Histological Study, 77-5667
- Mouth Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-5571
 - Hamster, 77-5571
 - Histological Study, 77-5571
- Nasopharyngeal Neoplasms
 - Antibodies, Viral, 77-5822
 - Neoplasm Transplantation, 77-5859
 - Virus, Epstein-Barr, 77-5459, 77-5822, 77-5823 77-5824, 77-5934
- Nickel
 - Rat, 77-5635
- Nose Neoplasms
 - Epidemiology, 77-5950
- Prostatic Neoplasms
 - Tissue Culture, 77-5915
- Skin Neoplasms
 - Arsenic, 77-5637
 - Fluorolone Acetonide, 77-5540
 - Fluocinolone Acetonide, 77-5540
 - 12-*O*-Tetradecanoylphorbol-13-acetate, 77-5540
- Stomach Neoplasms
 - Ataxia Telangiectasia, 77-5440
- Thyroid Neoplasms
 - Calcium Radioisotopes, 77-5665
 - Radiation, Ionizing, 77-5687
 - Strontium Radioisotopes, 77-5665
- Ureteral Neoplasms
 - Aryl Hydrocarbon Hydroxylases, 77-5589
- Virus, Feline Leukemia
 - RNA, Viral, 77-5715
 - Viral Proteins, 77-5715
- Virus, RD-114
 - RNA, Viral, 77-5715
 - Viral Proteins, 77-5715
- Carcinoma, Alveolar Cell**
 - see Carcinoma, Bronchiolar
- Carcinoma, Basal Cell**
 - Medulloblastoma
 - Review, 77-5439
 - Skin Neoplasms

Carcinoma, Basal Cell (cont'd)

- Xeroderma Pigmentosum, 77-5434
- Carcinoma, Bronchogenic**
 - Epidemiology
 - Diagnosis and Prognosis, 77-5941
 - Lung Neoplasms
 - Radiation, Ionizing, 77-5667
- Carcinoma, Epidermoid**
 - Lung Neoplasms
 - Radiation, Ionizing, 77-5667
 - Radon, 77-5419
 - Nose Neoplasms
 - Epidemiology, 77-5950
 - Paranasal Sinus Neoplasms
 - Cesium Chloride, 77-5666
 - Skin Neoplasms
 - Xeroderma Pigmentosum, 77-5434
 - Stomach Neoplasms
 - Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-, 77-5462
 - Urethral Neoplasms
 - Case Report, 77-5916
 - Urethra Stricture, 77-5916
 - Uterine Neoplasms
 - Diagnosis and Prognosis, 77-5910
- Carcinoma In Situ**
 - Cervix Neoplasms
 - Ultrastructural Study, 77-5911
- Carcinoma, Small Cell**
 - see Carcinoma; Carcinoma, Bronchogenic
- Carcinoma, Squamous Cell**
 - see Carcinoma, Epidermoid
- Carcinoma, Transitional Cell**
 - Urogenital Neoplasms
 - Genetics, 77-5936
- Cell Adhesion**
 - Cell Transformation, Neoplastic
 - Growth Substances, 77-5972
 - HeLa Cells
 - Agar, 77-5974
 - Pentadecan-2-one, 77-5974
 - Virus, SV40
 - Cell Transformation, Neoplastic, 77-5972
- Cell Aggregation**
 - Virus, Moloney Murine Leukemia
 - Temperature Sensitive Mutants, 77-5742
- Cell Differentiation**
 - Cervix Neoplasms
 - Metaplasia, 77-5453
 - Cervix Uteri
 - Mucus, 77-5453
 - Granulocytes
 - Cells, Cultured, 77-5963
 - Leukemia, Lymphocytic
 - Immune Serums, 77-5740
 - Macrophages
 - Cells, Cultured, 77-5963
 - Radiation
 - Carcinogenesis Model, Review, 77-5432
 - Sebaceous Gland Neoplasms
 - Cells, Cultured, 77-5975
 - Lipids, 77-5975
 - Teratoid Tumor
 - Ultrastructural Study, 77-5914

Cell Division

- Arsenic
 - Lymphocytes, 77-5640
- Breast Neoplasms
 - Cells, Cultured, 77-5960
 - Culture Media, 77-5971
 - Growth Substances, 77-5971
 - Protons, 77-5960
- Cell Transformation, Neoplastic
 - Models, Theoretical, 77-5967
- Cytochalasin B
 - Cell Transformation, Neoplastic, 77-5973
 - Fibroblasts, 77-5973
- Mammary Neoplasms, Experimental
 - Aldosterone, 77-5995
 - Corticosterone, 77-5995
 - Cortisol, 77-5995
 - Estradiol, 77-5995
 - Progesterone, 77-5995
- Prostate
 - Tissue Culture, 77-5915
- Prostatic Neoplasms
 - Tissue Culture, 77-5915
- Radiation, Ionizing
 - Interferon, 77-5684
- Virus, SV40
 - Cytochalasin B, 77-5973

Cell Membrane

- 1-Butanol, 2-Amino-
 - Lipids, 77-5706
- Cell Transformation, Neoplastic
 - Glycoproteins, 77-5969
 - Proteins, 77-5748, 77-5893
- Cells, Cultured
 - Plant Agglutinins, 77-5979
- Choline
 - Lipids, 77-5706
- Colonic Neoplasms
 - Glycoproteins, Review, 77-5450
- Ethanol, 2-Amino-
 - Lipids, 77-5706
- Ethanol, 2-Dimethylamino-
 - Lipids, 77-5706
- Ethanol, 2-(Methylamino)-
 - Lipids, 77-5706
- Glycoproteins
 - Isolation and Characterization, 77-5969
- Glucose, 2-Deoxy-
 - Metabolism, 77-5618
- Glycoproteins
 - Isolation and Characterization, 77-5980, 77-5981
- Leukemia
 - Lipids, 77-5998
 - B-Lymphocytes, 77-5663
 - T-Lymphocytes, 77-5663
- Lipids
 - Cells, Cultured, 77-5706
- Liver Neoplasms
 - Glycoproteins, 77-5981
- Mammary Neoplasms, Experimental
 - Glycoproteins, 77-5980
- Plant Agglutinins
 - Binding, 77-5979
- Proteins
 - Isolation and Characterization, 77-5893
- Virus, Feline Leukemia
 - Antigens, Viral, 77-5717

Cell Membrane (cont'd)

- Virus, Gross Murine Leukemia
 - Antigens, Viral, 77-5738
- Virus, Hamster Sarcoma
 - Cell Transformation, Neoplastic, 77-5774
- Virus, Radiation Leukemia
 - Antigens, Viral, 77-5738
- Virus, Rous-Associated
 - Binding, 77-5707
- Virus, Rous Sarcoma
 - Cells, Cultured, 77-5706
 - Lipids, 77-5706

Cell Nucleus

- Benzene
 - RNA, 77-5551
- Benzo(a)pyrene
 - RNA, 77-5551

Cell Transformation, Neoplastic

- Aging
 - Cells, Cultured, 77-5988
 - Embryo, Mouse, 77-5988
- Alpha Particles
 - Dose-Response Study, 77-5697
- Benz(a)anthracene, 7,12-Dimethyl-
 - Karyotyping, 77-5630
- Benz(a)anthracene, 7-Methyl-
 - Carcinogenic Metabolite, 77-5580
- Benzo(a)pyrene
 - Carcinogenic Metabolite, 77-5562
 - Cell-Cycle Kinetics, 77-5968
 - Fibrinolysis, 77-5556
 - Karyotyping, 77-5630
 - Phosphoinositides, 77-5968
 - Virus, Hamster C-Type RNA Tumor, 77-5773
- Carcinogen, Environmental
 - Animal Model, Fish, Review, 77-5405
- Cell Division
 - Models, Theoretical, 77-5967
- Cell Membrane
 - Glycoproteins, 77-5969
 - Proteins, 77-5748, 77-5893
- Cholanthrene, 3-Methyl-
 - Skin, 77-5585
- Chromosomes
 - Cells, Cultured, 77-5905
- Cytochalasin B
 - Cell Division, 77-5973
 - Cell Survival, 77-5973
- DNA
 - Carcinogenesis Model, Review, 77-5432
- Ethyl Alcohol
 - Growth, 77-5782
- Glucose, 2-Deoxy-
 - Lactic Acid, 77-5618
 - Metabolism, 77-5618
 - Temperature Sensitive Mutants, 77-5618
- Growth Substances
 - Cell Adhesion, 77-5972
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Karyotyping, 77-5630
- Hybrid Cells
 - Methods, 77-5428
- Hycanthone
 - Carcinogenic Potential, 77-5534
 - Virus, Rauscher Murine Leukemia, 77-5534
- Lucanthone

Cell Transformation, Neoplastic (cont'd)

- Carcinogenic Potential, 77-5534
- Virus, Rauscher Murine Leukemia, 77-5534
- Neoplasms, Experimental
 - Isolation and Characterization, 77-5969
- Oligopeptides
 - Bladder Neoplasms, 77-5606
- Prednisolone
 - Growth, 77-5782
- Radiation, Ionizing
 - Interferon, 77-5684
- Sarcoma
 - RNA, 77-5704
 - Virus, Rous Sarcoma, 77-5704
- Urea, Ethyl Nitroso-
 - Transplacental Carcinogenesis, 77-5615
- Virus, Avian Sarcoma
 - Antigens, Viral, 77-5710
- Virus, C-Type RNA Tumor
 - Cholanthrene, 3-Methyl-, 77-5583
 - Quinoline, 4-Nitro-, 1-Oxide, 77-5583
 - Rat, 77-5583
- Virus, Epstein-Barr
 - DNA, Viral, 77-5826
 - Nucleic Acid Hybridization, 77-5826
- Virus, Friend Murine Leukemia
 - Antigens, Viral, 77-5767
 - Glycoproteins, 77-5767
 - Ultrastructural Study, 77-5767
- Virus, Hamster Sarcoma
 - Cell Membrane, 77-5774
 - Peptides, 77-5774
- Virus, Herpes Simplex
 - Histological Study, 77-5816
- Virus, Herpes Simplex 1
 - Reverse Transcriptase, 77-5812
- Virus, Herpes Simplex 2
 - Reverse Transcriptase, 77-5812
- Virus, Kirsten Murine Sarcoma
 - Adenosine Cyclic 3',5' Monophosphate, 77-5748
 - Collagen, 77-5747
 - Epithelial Cells, 77-5749
 - Liver, Rat, 77-5749
- Virus, Moloney Murine Leukemia
 - Immune Serums, 77-5860
- Virus, Moloney Murine Sarcoma
 - Collagen, 77-5747
 - DNA, Viral, 77-5744
- Virus, Moloney Murine Sarcoma-Leukemia
 - Temperature Sensitive Mutants, 77-5743
- Virus, Polyoma
 - Cell-Cycle Kinetics, 77-5698
 - DNA, Viral, 77-5760
 - Histological Study, 77-5698
- Virus, Rous Sarcoma
 - Adenosine Deaminase, 77-5702
 - Antigens, Viral, 77-5708, 77-5711
 - Cell Cycle-Kinetics, 77-5698
 - Histological Study, 77-5698, 77-5708
- Virus, SV40
 - Cell Adhesion, 77-5972
 - Cell-Cycle Kinetics, 77-5968
 - Clone Cells, 77-5783
 - Insulin, 77-5788
 - Isolation and Characterization, 77-5792
 - Karyotyping, 77-5783
 - Phosphoinositides, 77-5968

Cells, Cultured

- Acetamide, *N*-Fluorenyl-
 - Carcinogenic Metabolite, 77-5469
- Aging
 - Cell Transformation, Neoplastic, 77-5988
 - Models, Theoretical, 77-5965
 - RNA Replication, 77-5988
- Aryl Hydrocarbon Hydroxylases
 - Enzymatic Activity, 77-5588
- Asbestos
 - Histological Study, 77-5646
 - Toxicology, 77-5410
- Bactopeptone
 - Growth Substances, 77-5966
- Benz(a)anthracene, 7-Bromomethyl-
 - DNA Repair, 77-5581
- Benz(a)anthracene, 7,12-Dimethyl-
 - Metabolism, 77-5570
- Benz(a)anthracene, 7-Methyl-
 - Mutagenic Activity, 77-5580
- Benzo(a)pyrene
 - Fibrinolysis, 77-5556
 - Liver Neoplasms, 77-5559
 - Metabolism, 77-5559, 77-5570
- Bladder
 - Histological Study, 77-5976
 - Putrescine, 77-5976
 - Rat, 77-5976
 - Spermidine, 77-5976
 - Spermine, 77-5976
- Breast Neoplasms
 - Cell Division, 77-5960
 - Collagen, 77-5983
 - Models, Biological, 77-5576
 - Nuclear Magnetic Resonance Properties, 77-5960
- Burkitt's Lymphoma
 - Antigens, Viral, 77-5828
- Caffeine
 - Chromosome Aberrations, 77-5629
- Cell Differentiation
 - Granulocytes, 77-5963
 - Macrophages, 77-5963
- Cell Membrane
 - Plant Agglutinins, 77-5979
- Chondrosarcoma
 - Antigens, Neoplasm, 77-5881
- Choriocarcinoma
 - Carcinoembryonic Antigen, 77-5970
 - Gonadotropins, Chorionic, 77-5970
- Chromosome Aberrations
 - Benzo(a)pyrene, 77-5631
 - Caffeine, 77-5631
 - Cholanthrene, 3-Methyl-, 77-5631
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-5631
 - Pyrene, 77-5631
 - Quinoline, 4-Nitro-, 1-Oxide, 77-5631
- Chromosomes
 - Cell Transformation, Neoplastic, 77-5905
- Colonic Neoplasms
 - Carcinoembryonic Antigen, 77-5970
- Cyclophosphamide
 - Metabolism, 77-5533
- Diethylamine, *N*-Nitroso-
 - Liver Neoplasms, 77-5919
- Dimethylamine, *N*-Nitroso-
 - Mutagenic Activity, 77-5681
- DNA Repair

Cells, Cultured (cont'd)

- Benzo(a)pyrene, 77-5673
- Radiation, Ionizing, 77-5673
- Ultraviolet Rays, 77-5675
- Urea, Methyl Nitroso-, 77-5616
- Virus, Herpes Simplex 2, 77-5814
- Ethyl Alcohol
 - Growth, 77-5782
- Fibrosarcoma
 - Antigens, Neoplasm, 77-5881
 - Virus, Kirsten Murine Sarcoma, 77-5749
- 2-Furaldehyde, 5-Nitro-, Semicarbazone
 - Metabolism, 77-5625
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Mutagenic Activity, 77-5536, 77-5537, 77-5580, 77-5680, 77-5681
- ICR 191
 - Mutagenic Activity, 77-5680, 77-5681
- Leukemia
 - Histones, 77-5730
- Lipids
 - Cell Membrane, 77-5706
 - Histological Study, 77-5706
- Lymphocytes
 - Chromosome Aberrations, 77-5628
- Melanoma
 - Peptide Hydrolases, 77-5985
- Metals
 - Toxicology, 77-5410
- Methanesulfonic Acid, Ethyl Ester
 - Chromosome Aberrations, 77-5629
 - Mutagenic Activity, 77-5632, 77-5680, 77-5681
- Methanesulfonic Acid, Methyl Ester
 - Chromosome Aberrations, 77-5629
- Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)
 - Mutagenic Activity, 77-5536
- Methanol, (Methyl-*ONN*-azoxy)-
 - Mutagenic Activity, 77-5537
- Mitomycin C
 - Chromosome Aberrations, 77-5629
- 1,4-Naphthoquinone, 2-Methyl-
 - Metabolism, 77-5625
- Phorbol 12,3-Didecanoate
 - DNA Replication, 77-5539
- Phosphine Sulfide, Tris(1-aziridinyl)-
 - Chromosome Aberrations, 77-5629
- Platinum, Diaminedichloro-, *cis*-
 - Mutagenic Activity, 77-5681
- Prednisolone
 - Growth, 77-5782
- Prolactin
 - Virus Replication, 77-5754
- Psoralen, 8-Methoxy-
 - Ultraviolet Rays, 77-5668
- Quinoline, 4-Nitro-, 1-Oxide
 - Chromosome Aberrations, 77-5629
 - Metabolism, 77-5625
- Radiation, Ionizing
 - Azaguanine Resistance, 77-5652
 - Mutagenic Activity, 77-5649, 77-5652, 77-5681
- Sarcoma
 - Glucosaminidase, 77-5573
 - Lysosomes, 77-5573
 - Virus, Kirsten Murine Sarcoma, 77-5749
- Sarcoma, Mast Cell
 - Immunosuppression, 77-5861
- Sebaceous Gland Neoplasms

Cells, Cultured (cont'd)

- Cell Differentiation, 77-5975
- Somatotropin
 - Virus Replication, 77-5754
- Sulfuric Acid, Dimethyl Ester
 - Chromosome Aberrations, 77-5629
- Teratoid Tumor
 - Virus, SV40, 77-5793
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - DNA Replication, 77-5539
 - Mutagenic Activity, 77-5536, 77-5537
- s*-Triazin-2(1*H*)-one, 4-Amino-1- β -*D*-ribofuranosyl-
 - Histological Study, 77-5532
- Ultraviolet Rays
 - Mutagenic Activity, 77-5679, 77-5680, 77-5681
- Urea, Ethyl Nitroso-
 - Fibrinolysis, 77-5612
- Urea, Methyl Nitroso-
 - Lung, 77-5619
- Uridine, 5-Bromo-2'-deoxy-
 - Mutagenic Activity, 77-5632
- Virus, Adeno
 - Antigens, Viral, 77-5724
- Virus, D-Type RNA Tumor
 - Antigens, Viral, 77-5851
 - DNA-RNA Hybridization, 77-5780
- Virus, Epstein-Barr
 - Antigens, Viral, 77-5820, 77-5822
 - Ultrastructural Study, 77-5819
- Virus, Friend Murine Leukemia
 - Antibodies, Viral, 77-5732
 - Lymphoma, 77-5750
- Virus, Herpes Simplex 1
 - RNA Polymerase, 77-5813
- Virus, Herpes Simplex 2
 - Thymidine Kinase, 77-5815
- Virus, Moloney Murine Sarcoma
 - Lymphoma, 77-5750
- Virus, Murine Leukemia
 - RNA Polymerase, 77-5763
- Virus, Rauscher Murine Leukemia
 - Virus Replication, 77-5726
- Virus, Rous-Associated
 - RNA, Viral, 77-5705
- Virus, Rous Sarcoma
 - Cell Membrane, 77-5706
 - RNA, Viral, 77-5705
- Virus, Sendai
 - Antigens, Viral, 77-5820
- Virus, Simian Sarcoma-Associated
 - Virus Replication, 77-5778
- Virus, SV40
 - Plasminogen, 77-5784
- Virus, SV40
 - Mutagenic Activity, 77-5796
- Cellular Inclusions
 - Virus, Parvo
 - Antigens, Viral, 77-5798
- Cellulose, Methyl Ether
 - Virus, SV40
 - Clone Cells, 77-5783
- Cervix Neoplasms
 - Carcinoma
 - Virus, Herpes Simplex 2, 77-5422
 - Carcinoma In Situ
 - Ultrastructural Study, 77-5911

- Cervix Neoplasms (cont'd)**
 Chromosome Abnormalities
 Chromosomes, Human, 1-3, 77-5907
 Contraceptives, Oral
 Estrogens, 77-5413
 Review, 77-5413
 Epidemiology
 Review, 77-5457
 Hysterectomy
 Epidemiology, 77-5928
 Metaplasia
 Cell Differentiation, 77-5453
 Mucus, 77-5453
 Neoplasm Metastasis
 Ultrastructural Study, 77-5911
 Parity
 Epidemiology, Nigeria, 77-5927
 Precancerous Conditions
 Ultrastructural Study, 77-5911
 Sex Behavior
 Epidemiology, Nigeria, 77-5927
- Cervix Uteri**
 Carbenoxolone
 Mucosal Glycoproteins, Review, 77-5452
 Cell Differentiation
 Mucus, 77-5453
 Gastrointestinal System
 Carbenoxolone, 77-5452
- Cesium Chloride**
 Paranasal Sinus Neoplasms
 Carcinoma, Epidermoid, 77-5666
 Neoplasm Metastasis, 77-5666
- Cesium Radioisotopes**
 Thyroid Neoplasms
 Adenoma, 77-5665
 Strontium Radioisotopes, 77-5665
- Chlordiazepoxide**
 Nitrous Acid, Sodium Salt
 Carcinogenic Potential, Rat, 77-5602
- Chloroform**
 Neoplasms
 Fish, 77-5958
- Cholangiocarcinoma**
 see Cholangioma
- Cholangioma**
 C.I. Direct Violet 100
 Rat, 77-5478
- Cholanthrene, 11,12-Dihydro-11,12-epoxy-3-methyl-**
 DNA
 Binding, Mouse Embryo, 77-5584
 Carcinogenic Metabolite, 77-5584
 Liver
 Hydro-Lyases, 77-5543
- Cholanthrene, 3-Methyl-**
 Aryl Hydrocarbon Hydroxylases
 Genetics, Mouse, 77-5592
 Liver, Lung, Mouse, 77-5592
 NADPH, 77-5544
 Benzo(a)pyrene
 Metabolism, 77-5566
 Cells, Cultured
- Cholanthrene, 3-Methyl- (cont'd)**
 Chromosome Aberrations, 77-5631
 Cytochrome P-448
 Microsomes, Liver, 77-5554
 DNA
 Binding, 77-5544, 77-5548
 Binding, Mouse Embryo, 77-5584
 Carcinogenic Metabolite, 77-5584
 Glioblastoma Multiforme
 Mouse, 77-5766
 Liver
 Histological Study, Rat, 77-5547
 Ultrastructural Study, Rat, 77-5547
 Lymphocytes
 Aryl Hydrocarbon Hydroxylases, 77-5588
 Neoplasms, Experimental
 Stress, 77-5586
 Temperature, 77-5586
 Pancreatic Neoplasms
 Epidemiology, Review, 77-5449
 Phorbol 12,13-Didecanoate
 DNA Replication, 77-5539
 Rhabdomyosarcoma
 Mouse, 77-5863
 Sarcoma
 Carcinoembryonic Antigen, 77-5869
 Chromosomes, 77-5909
 Immune Response, 77-5854, 77-5855, 77-5886
 Immunologic Technics, 77-5869
 Mouse, 77-5886
 Teratoid Tumor, 77-5869
 Skin
 Cell Transformation, Neoplastic, 77-5585
 Histological Study, 77-5587
 Mouse, 77-5587
 Ribosomes, 77-5587
 Ultrastructural Study, Mouse, 77-5585
 Skin Neoplasms
 5,6-Benzoflavone, 77-5548
 7,8-Benzoflavone, 77-5548
 Succinate Dehydrogenase
 Enzymatic Activity, 77-5546
 Liver, 77-5546
 12- α -Tetradecanoylphorbol-13-acetate
 DNA Replication, 77-5539
 Virus, C-Type RNA Tumor
 Cell Transformation, Neoplastic, 77-5583
 Virus, Murine Sarcoma
 Carcinogenic Activity, 77-5866
 Immune Response, 77-5866
- Cholestyramine**
 Intestinal Neoplasms
 Methane, Azoxy-, 77-5474
- Choline**
 Lipids
 Cell Membrane, 77-5706
- Choline, Chloride, Carbamate**
 Hepatoma
 Butyric Acid, 2-Amino-4-(ethylthio)-, 77-5499
- Chondrosarcoma**
 Antigens, Neoplasm
 Cells, Cultured, 77-5881
 Culture Media, 77-5881
- Choriocarcinoma**
 Cells, Cultured

Choriocarcinoma (cont'd)

- Carcinoembryonic Antigen, 77-5970
- Gonadotropins, Chorionic, 77-5970

Chromatin

- DNA Repair
 - Methanesulfonic Acid, Methyl Ester, 77-5626
- Virus, Parvo
 - Antigens, Viral, 77-5798
- Virus, SV40
 - Antigens, Viral, 77-5801

Chromium

- DNA Replication
 - Carcinogenic Activity, 77-5634
 - Mutagenic Activity, 77-5634
- Neoplasms, Experimental
 - Trace Elements, Review, 77-5412
- Occupational Hazard
 - Trace Elements, Review, 77-5412

Chromium, Dichlorodioxo-

- Cytochrome P-450
 - Enzyme Activation, 77-5491
 - Molecular Orbital Calculations, 77-5491

Chromosome Aberrations

- Anemia, Aplastic
 - Review, 77-5438
- Arsenic
 - Lymphocytes, 77-5639, 77-5640
 - Occupational Hazard, 77-5639
- Ataxia Telangiectasia
 - Review, 77-5438
- Benzo(a)pyrene
 - Lymphocytes, 77-5627
- Caffeine
 - Cells, Cultured, 77-5629
- Cells, Cultured
 - Benzo(a)pyrene, 77-5631
 - Caffeine, 77-5631
 - Cholanthrene, 3-Methyl-, 77-5631
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-5631
 - Pyrene, 77-5631
 - Quinoline, 4-Nitro-, 1-Oxide, 77-5631
- Cyclophosphamide
 - Drosophila melanogaster*, 77-5401
- Diethylamine, N-Nitroso-
 - Drosophila melanogaster*, 77-5401
 - Lymphocytes, 77-5627
- Dimethylamine, N-Nitroso-
 - Lymphocytes, 77-5627
- Ethylene, Chloro-
 - Drosophila melanogaster*, 77-5401
 - Epidemiology, 77-5496
- Ethylene Oxide
 - Rat, 77-5489
- Leukemia
 - Epidemiology, 77-5444
 - Review, 77-5435
- Leukemia, Lymphoblastic
 - Epidemiology, 77-5899
 - Review, 77-5431
- Leukemia, Myeloblastic
 - Genetics, 77-5441
 - Review, 77-5431
- Leukemia, Myelocytic
 - Review, 77-5431
- Lymphocytes

Chromosome Aberrations (cont'd)

- Actinomycin D, 77-5628
- Cells, Cultured, 77-5628
- Meningioma
 - Review, 77-5435
- Methanesulfonic Acid, Ethyl Ester
 - Cells, Cultured, 77-5629
 - Lymphocytes, 77-5627
- Methanesulfonic Acid, Methyl Ester
 - Cells, Cultured, 77-5629
 - Drosophila melanogaster*, 77-5401
 - Lymphocytes, 77-5627
- Mitomycin C
 - Cells, Cultured, 77-5629
 - Lymphocytes, 77-5627
- Mutagenic Activity, Review
 - Carcinogenic Potential, 77-5401
- Neoplasms
 - Models, Theoretical, 77-5430
- Neuroblastoma
 - Ultrastructural Study, 77-5902
- o*-Phenylenediamine, 4-Nitro-
 - Review, 77-5435
- Phosphine Sulfide, Tris(1-aziridinyl)-
 - Cells, Cultured, 77-5629
- Psoralen, 8-Methoxy-
 - Lymphocytes, 77-5672
- Quinoline, 4-Nitro-, 1-Oxide
 - Cells, Cultured, 77-5629
- Radiation, Ionizing
 - Dose-Response Study, 77-5650, 77-5696
 - Lymphocyte Transformation, 77-5650
 - Lymphocytes, 77-5650
 - Review, 77-5435
 - Vicia faba*, 77-5696
- Skin Neoplasms
 - Arsenic, 77-5640
- Sulfuric Acid, Dimethyl Ester
 - Cells, Cultured, 77-5629
- Triazene, 3,3-Dimethyl-1-(*m*-pyridyl)-
 - Drosophila melanogaster*, 77-5401
- Ultraviolet Rays
 - Lymphocytes, 77-5672
- Virus, SV40
 - Review, 77-5435
- Xeroderma Pigmentosum
 - Review, 77-5438

Chromosome Abnormalities

- Leukemia
 - Karyotyping, 77-5900
- Leukemia, Lymphoblastic
 - Case Report, 77-5898
- Radiation, Ionizing
 - Vicia faba*, 77-5696

Chromosomes

- Cell Transformation, Neoplastic
 - Cells, Cultured, 77-5905
- Leukemia, Myeloblastic
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-5575
- Proteins
 - Antigens, Neoplasm, 77-5664
- Sarcoma
 - Cell-Cycle Kinetics, 77-5909
 - Cholanthrene, 3-Methyl-, 77-5909

Chromosomes, Human, 21-22

- Leukemia, Myelocytic

Chromosomes, Human, 21-22 (cont'd)
 Transplantation, Heterologous, 77-5858

Chromyl Chloride
 see Chromium, Dichlorodioxo-

Chrysene
 Deuterium
 Synthesis, 77-5567

Clone Cells
 Virus, SV40
 Agglutination, 77-5783
 Cell Transformation, Neoplastic, 77-5783
 Cellulose, Methyl Ether, 77-5783
 Concanavalin A, 77-5783
 DNA, 77-5783

Cobalt
 DNA Replication
 Carcinogenic Activity, 77-5634
 Mutagenic Activity, 77-5634
 Neoplasms, Experimental
 Trace Elements, Review, 77-5412

Cold
 Radiation, Ionizing
 Thyroid Gland, 77-5686

Coliphages
 Benz(a)anthracene
 DNA, 77-5545
 RNA, 77-5545
 Benz(a)anthracene, 5,6-Dihydro-5,6-epoxy-
 DNA, 77-5545
 RNA, 77-5545
 Benz(a)anthracene, 7,12-Dimethyl-
 DNA, 77-5545
 RNA, 77-5545
 Benz(a)anthracene, 12-Methyl-7-oxiranyl-
 RNA, 77-5545
 Benz(a)anthracene, 12-Methyl-7-oxiranyl-
 DNA, 77-5545
 Benzo(a)pyrene
 DNA, 77-5545
 RNA, 77-5545
 Phenanthrene
 DNA, 77-5545
 RNA, 77-5545
 Polycyclic Hydrocarbons
 DNA, 77-5545
 RNA, 77-5545

Collagen
 Breast Neoplasms
 Ascorbic Acid, 77-5983
 Cells, Cultured, 77-5983
 Isolation and Characterization, 77-5983
 Propionitrile, 3-Amino-, 77-5983
 Smoking
 Lung, 77-5594
 Virus, Kirsten Murine Sarcoma
 Cell Transformation, Neoplastic, 77-5747
 Virus, Moloney Murine Sarcoma
 Cell Transformation, Neoplastic, 77-5747

Colon
 Cell Cycle Kinetics
 Review, 77-5961

Colonic Neoplasms
 Adenocarcinoma

Colonic Neoplasms (cont'd)
 Carcinoembryonic Antigen, 77-5970
 Glycoproteins, Review, 77-5450

Breast Neoplasms
 Epidemiology, US, 77-5932

Carbohydrates
 Glycoproteins, Review, 77-5450

Carcinoma
 Carcinoembryonic Antigen, 77-5889
 Hydrazine, 1,2-Dimethyl-, Dihydrochloride, 77-5501
 Methane, 77-5476

Cell Membrane
 Glycoproteins, Review, 77-5450

Cells, Cultured
 Carcinoembryonic Antigen, 77-5970

Diet
 Epidemiology, 77-5460
 Polycyclic Hydrocarbons, 77-5460
 Review, 77-5460

Galactosamine
 Glycoproteins, Review, 77-5450

Genetics
 Epidemiology, 77-5904

Glycoproteins
 Isolation and Characterization, 77-5889

Hydrazine, 1,1-Dimethyl-
 Cereals, 77-5502
 Corn Oil, 77-5502
 Dietary Fats, 77-5502
 Histological Study, Rat, 77-5502

Hydrazine, 1,2-Dimethyl-, Dihydrochloride
 Cell Cycle Kinetics, 77-5501

Isoantigens
 Glycoproteins, Review, 77-5450

Complement
 Virus, Moloney Murine Leukemia
 Virus Replication, 77-5860

Concanavalin A
 Lymphocytes
 Aryl Hydrocarbon Hydroxylases, 77-5588
 Virus, SV40
 Clone Cells, 77-5783

Condylomata Acuminata
 Case Report
 Histological Study, 77-5844
 Ultrastructural Study, 77-5844
 Virus, Papova
 Case Report, 77-5844

Connective Tissue
 Plutonium Oxide
 Lung, 77-5661

Contact Inhibition
 Glioma
 Dexamethasone, 77-5987

Contraceptives, Oral
 Cervix Neoplasms
 Estrogens, 77-5413
 Review, 77-5413
 Liver Neoplasms
 Adenoma, 77-5523
 Epidemiology, 77-5525
 Mammary Neoplasms, Experimental
 Adenocarcinoma, 77-5526
 Adenoma, 77-5527

- Contraceptives, Oral (cont'd)**
 Dog, 77-5526
 Histological Study, 77-5526
 Monkey
 Histological Study, 77-5526
 Uterine Neoplasms
 Adenocarcinoma, 77-5413
 Review, 77-5413
- Corticosterone**
 Mammary Neoplasms, Experimental
 Cell Division, 77-5995
- Corticotropin**
 Neoplasm Transplantation
 Mouse, 77-5528
- Cortisol**
 Mammary Neoplasms, Experimental
 Cell Division, 77-5995
 Neoplasm Transplantation
 Mouse, 77-5528
- Corynebacterium parvum***
 Mammary Neoplasms, Experimental
 Benz(a)anthracene, 7,12-Dimethyl-, 77-5579
- Coumarin**
 Liver
 Hydroxylases, 77-5569
 Metabolism, 77-5569
- Coumarin, 7-Ethoxy-**
 Liver
 Metabolism, 77-5569
- p*-Cresol, 2,6-Di-*tert*-butyl-**
 Dimethylamine, *N*-Nitroso-
 Rat, 77-5610
- Croton Oil**
 Tongue Neoplasms
 Quinoline, 4-Nitro-, 1-Oxide, 77-5624
- Cumin Oil**
 Liver Regeneration
 Rat, 77-5516
- Cycloheximide**
 Tyrosine
 Melanin, 77-5986
- Cyclophosphamide**
 Cells, Cultured
 Metabolism, 77-5533
 Chromosome Aberrations
Drosophila melanogaster, 77-5401
- Cyprosterone Acetate**
 Liver Neoplasms
 Adenoma, 77-5523
- Cysteine**
 Retronecine, 3,8-Didehydro-
 Binding, 77-5505
- Cytochalasin B**
 Cell Division
 Cell Transformation, Neoplastic, 77-5973
 Cell Survival
 Cell Transformation, Neoplastic, 77-5973
 Fibroblasts
 Cell Division, 77-5973
 Cell Survival, 77-5973
- Cytochalasin B (cont'd)**
 Virus, SV40
 Cell Division, 77-5973
- Cytochrome Oxidase**
 Arsenic Acid, Sodium Salt
 Mitochondria, Liver, 77-5642
- Cytochrome P-448**
 Benzo(a)pyrene
 Metabolism, 77-5554
 Cholanthrene, 3-Methyl-
 Microsomes, Liver, 77-5554
 Sulfhydryl Compounds
 Metabolism, 77-5554
- Cytochrome P-450**
 Benzo(a)pyrene
 Microsomes, Liver, 77-5555
 Chromium, Dichlorodioxo-
 Enzyme Activation, 77-5491
 Molecular Orbital Calculations, 77-5491
 Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-
 Dietary Proteins, 77-5492
 Retinol, 77-5492
 Peroxidases
 Enzyme Activation, 77-5491
 Molecular Orbital Calculations, 77-5491
 Peroxyacetic Acid, Trifluoro-
 Enzyme Activation, 77-5491
 Molecular Orbital Calculations, 77-5491
 Trout
 Isolation and Characterization, 77-5553
- Cytochromes**
 Benzo(a)pyrene
 Microsomes, Liver, 77-5555
- Cytosine, 1- β -*D*-Arabinofuranosyl-**
 DNA Polymerase
 DNA Replication, 77-5758
- p,p*-DDT**
 see Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-
- Deuterium**
 Benz(a)anthracene
 Synthesis, 77-5567
 Benzo(a)pyrene
 Synthesis, 77-5567
 Carbazole
 Synthesis, 77-5567
 Chrysene
 Synthesis, 77-5567
 Fluoranthene
 Synthesis, 77-5567
 Pyrene
 Synthesis, 77-5567
- Dexamethasone**
 Glioma
 Contact Inhibition, 77-5987
 DNA Replication, 77-5987
 Virus, Mason-Pfizer Monkey
 Reverse Transcriptase, 77-5775
 Virus Replication, 77-5775
- Diallylnitrosamine**
 see 2-Propen-1-amine, *N*-2-Propenyl-*N*-nitroso-
- Dibenz(a,h)anthracene**
 Aryl Hydrocarbon Hydroxylases

Dibenz(a,h)anthracene (cont'd)

NADPH, 77-5544

DNA

Binding, 77-5544, 77-5548

Liver

Histological Study, Rat, 77-5547
Ultrastructural Study, Rat, 77-5547

Skin Neoplasms

5,6-Benzoflavone, 77-5548
7,8-Benzoflavone, 77-5548

Succinate Dehydrogenase

Enzymatic Activity, 77-5546

Dibenz(a,h)anthracene, 5,6-Dihydro-5,6-epoxy-

Liver

Hydro-Lyases, 77-5543

Dichromic Acid, Disodium Salt

Carcinogenic Potential

Mouse, 77-5597

Diet

Colonic Neoplasms

Epidemiology, 77-5460
Polycyclic Hydrocarbons, 77-5460
Review, 77-5460

DNA Replication

Liver, 77-5991

Esophageal Neoplasms

Epidemiology, 77-5940
Epidemiology, Turkey, 77-5939
Tea, 77-5939

Mycotoxins

Review, 77-5460

Ornithine Decarboxylase

Enzymatic Activity, 77-5991

Polyamines

DNA Replication, 77-5991

1,3-Propanediamine

DNA Replication, 77-5991

Stomach Neoplasms

Epidemiology, 77-5460
Epidemiology, Turkey, 77-5939
Nitrosamines, 77-5460
Review, 77-5460**Dietary Fats**

Ultraviolet Rays

Carcinogenic Activity, Review, 77-5421

Dietary ProteinsEthane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-
Cytochrome P-450, 77-5492**Diethylamine, N-Nitroso-**

Bronchi

DNA, Binding, 77-5603
Metabolism, 77-5603

Chromosome Aberrations

Drosophila melanogaster, 77-5401

Hepatoma

Acetamide, *N*-Fluoren-2-yl-, 77-5920
Ultrastructural Study, Monkey, 77-5608
Virus, Hepatitis, 77-5608

Liver Neoplasms

Cells, Cultured, 77-5919
Histological Study, 77-5919
Immunity, 77-5427

Lymphocytes

Cell-Cycle Kinetics, 77-5627

Diethylamine, N-Nitroso- (cont'd)

Chromosome Aberrations, 77-5627

Nitrous Acid

Saccharomycopsis lipolytica, 77-5604

Virus, Hepatitis

Co-carcinogenic Activity, Monkey, 77-5608

Digestive System Neoplasms

Arsenic Trioxide

Occupational Hazard, 77-5636

Ethylene, Chloro- Polymer

Epidemiology, 77-5946

Gold Coast

Epidemiology, 77-5937

Hormones

Review, 77-5415

Liver Cirrhosis

Epidemiology, 77-5943

Occupational Hazard

Epidemiology, 77-5946

Dimethylamine

Nitrous Acid, Sodium Salt

Nitrosamine Formation, 77-5610

Dimethylamine, N-Nitroso-

Antigens

Liver, 77-5482

Ascorbic Acid, Monosodium Salt

Rat, 77-5610

Benzylamine

Metabolism, 77-5609

Bronchi

DNA, Binding, 77-5603
Metabolism, 77-5603

Cells, Cultured

Mutagenic Activity, 77-5681

p-Cresol, 2,6-Di-*tert*-butyl-

Rat, 77-5610

Gallic Acid, Propyl Ester

Rat, 77-5610

Hydroquinone, *t*-Butyl-

Rat, 77-5610

Intestinal Neoplasms

Dose-Response Study, Rat, 77-5611

Kidney Neoplasms

Ascorbic Acid, 77-5599

Dose-Response Study, Rat, 77-5611

Rat, 77-5599

Liver

Rat, 77-5610

Liver Neoplasms

Ascorbic Acid, 77-5599

Rat, 77-5599

Lung Neoplasms

Ascorbic Acid, 77-5599

Dose-Response Study, Rat, 77-5611

Rat, 77-5599

Lymphocytes

Cell-Cycle Kinetics, 77-5627

Chromosome Aberrations, 77-5627

Mixed Function Oxidases

Metabolism, 77-5609

Monoamine Oxidase

Metabolism, 77-5609

Nitrous Acid

Saccharomycopsis lipolytica, 77-5604

Phenol, (1,1-Dimethylethyl)-4-methoxy-

Rat, 77-5610

- Dipentylamine, *N*-Nitroso-**
Nitrous Acid
Saccharomycopsis lipolytica, 77-5604
- Dipropylamine, 2,2'-Dioxo-*N*-nitroso-**
Pancreatic Neoplasms
Carcinogenic Activity, Hamster, 77-5607
- Disgerminoma**
Testicular Neoplasms
Case Report, 77-5690
- DNA**
Acetamide, *N*-(Acetyloxy)-*N*-fluorene-2-yl-
Binding, 77-5468
Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-
Binding, 77-5463
Aryl Hydrocarbon Hydroxylases
Binding, 77-5544
Benz(a)anthracene
Coliphages, 77-5545
Benz(a)anthracene, 7-Bromomethyl-
Binding, 77-5582
Benz(a)anthracene, 5,6-Dihydro-5,6-epoxy-
Coliphages, 77-5545
Benz(a)anthracene, 7,12-Dimethyl-
Binding, 77-5544, 77-5548, 77-5570, 77-5576
Coliphages, 77-5545
Benz(a)anthracene, 12-Methyl-7-oxiranyl-
Coliphages, 77-5545
Benzo(a)pyrene
Binding, 77-5544, 77-5557, 77-5565, 77-5568
77-5570
Coliphages, 77-5545
RNA, 77-5557
Benzo(b)triphenylene
Binding, 77-5544
Carcinogen, Chemical
Carcinogenesis Model, Review, 77-5432
Cell Transformation, Neoplastic
Carcinogenesis Model, Review, 77-5432
Cholanthrene, 11,12-Dihydro-11,12-epoxy-3-methyl-
Binding, Mouse Embryo, 77-5584
Carcinogenic Metabolite, 77-5584
Cholanthrene, 3-Methyl-
Binding, 77-5544, 77-5548
Binding, Mouse Embryo, 77-5584
Carcinogenic Metabolite, 77-5584
Dibenz(a,h)anthracene
Binding, 77-5544, 77-5548
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Mitochondria, 77-5623
Heat
Binding, Acridine, 77-5676
Epidermal Cells, 77-5676
Hydrazine, 1,2-Dimethyl-
Alkylation, Rat, 77-5503
Purine, 2-Amino-6-methoxy-, 77-5503
Leukemia, Myeloblastic
Benz(a)anthracene, 7,12-Dimethyl-, 77-5575
Methanesulfonic Acid, Methyl Ester
Alkylation, 77-5990
NADPH
Binding, 77-5544
Oncogenic Viruses
Carcinogenesis Model, Review, 77-5432
Phenanthrene
Coliphages, 77-5545
Polycyclic Hydrocarbons
- DNA (cont'd)**
Coliphages, 77-5545
Psoralen, 8-Methoxy-
Binding, 77-5668
Photoproducts, 77-5671
Quinoline-1-oxide, 4-Nitro-
Mitochondria, 77-5623
Radiation
Carcinogenesis Model, Review, 77-5432
Ultraviolet Rays
Binding, Acridine, 77-5676
Epidermal Cells, 77-5676
Psoralen, 8-Methoxy-, 77-5671
Virus, SV40
Antigens, Viral, 77-5801
Clone Cells, 77-5783
- DNA, Bacterial**
Plant Tumors
Agrobacterium tumefaciens, 77-6000
- DNA Nucleotidyltransferases**
Virus, Adeno 2
DNA Replication, 77-5840
HeLa Cells, 77-5840
Isolation and Characterization, 77-5840
- DNA Polymerase**
DNA Replication
Cytosine, 1- β -*D*-Arabinofuranosyl-, 77-5758
DNA, Viral, 77-5791
Urea, Hydroxy-, 77-5758
Uridine, 2'-Deoxy-5-fluoro-, 77-5758
Exonucleases
Enzymatic Activity, 77-5535
Lymphosarcoma
Fish, 77-5699
Isolation and Characterization, 77-5699
Virus, Polyoma
Enzymatic Activity, 77-5758
- DNA Repair**
Acetaldehyde, Chloro-
Quantitation Method, Review, 77-5411
Ataxia Telangiectasia
Radiation, Ionizing, 77-5433
Benz(a)anthracene, 7-Bromomethyl-
Cells, Cultured, 77-5581
Benzo(a)pyrene
Cells, Cultured, 77-5673
Caffeine, 77-5582
Mutagenic Activity, 77-5679
Carcinogen, Environmental
Carcinogenic Activity, Review, 77-5411
Mutagenic Activity, Review, 77-5411
Quantitation Method, Review, 77-5411
Escherichia coli
Lysogeny, 77-5677
Ethylene, 1,2-Dibromo-
Rat, 77-5487
Methanesulfonic Acid, Methyl Ester
Chromatin, 77-5626
Endonuclease, 77-5990
Glycoside Hydrolases, 77-5990
Mutagens
Quantitation Method, Review, 77-5411
Progeria
Radiation, Ionizing, 77-5433
Radiation, Ionizing

NA Repair (cont'd)

- Cells, Cultured, 77-5673
- Mouse, 77-5674
- Ultraviolet Rays
 - Carcinogenic Activity, Review, 77-5421
 - Cells, Cultured, 77-5675
 - Escherichia coli*, 77-5677
- Urea, Methyl Nitroso-
 - Cells, Cultured, 77-5616
- Virus, Herpes Simplex 2
 - Cells, Cultured, 77-5814
 - Estradiol, 77-5814
- Virus, Rous Sarcoma
 - DNA Replication, 77-5703
 - DNA-RNA Hybridization, 77-5703
 - Quinoline, 4-Nitro-, 1-Oxide, 77-5703
 - Ultraviolet Rays, 77-5703
- Xeroderma Pigmentosum
 - Ultraviolet Rays, 77-5433, 77-5434

NA Replication

- Arsenic
 - Lymphocytes, 77-5640
- Beryllium
 - Carcinogenic Activity, 77-5634
 - Mutagenic Activity, 77-5634
- Cadmium
 - Carcinogenic Activity, 77-5634
 - Mutagenic Activity, 77-5634
- Chromium
 - Carcinogenic Activity, 77-5634
 - Mutagenic Activity, 77-5634
- Cobalt
 - Carcinogenic Activity, 77-5634
 - Mutagenic Activity, 77-5634
- DNA Polymerase
 - Cytosine, 1- β -D-Arabinofuranosyl-, 77-5758
 - Urea, Hydroxy-, 77-5758
 - Uridine, 2'-Deoxy-5-fluoro-, 77-5758
- DNA, Viral
 - DNA Polymerase, 77-5791
- Fluclorolone Acetonide
 - Mouse, 77-5540
- Fluocinolone Acetonide
 - Mouse, 77-5540
- Glioma
 - Dexamethasone, 77-5987
- Lead
 - Carcinogenic Activity, 77-5634
 - Mutagenic Activity, 77-5634
- Liver
 - Diet, 77-5991
- Manganese
 - Carcinogenic Activity, 77-5634
 - Mutagenic Activity, 77-5634
- Nafenopin
 - Liver, Rat, 77-5531
- Nickel
 - Carcinogenic Activity, 77-5634
 - Mutagenic Activity, 77-5634
- Phorbol 12,13-Didecanoate
 - Cells, Cultured, 77-5539
 - Cholanthrene, 3-Methyl-, 77-5539
- Polyamines
 - Diet, 77-5991
 - Liver, 77-5991
- 1,3-Propanediamine
 - Diet, 77-5991

DNA Replication (cont'd)

- Silver
 - Carcinogenic Activity, 77-5634
 - Mutagenic Activity, 77-5634
- 12-O-Tetradecanoylphorbol-13-acetate
 - Cells, Cultured, 77-5539
 - Cholanthrene, 3-Methyl-, 77-5539
- Virus, Adeno 2
 - DNA Nucleotidyltransferases, 77-5840
 - DNA, Viral, 77-5839
 - Isolation and Characterization, 77-5839
- Virus, Epstein-Barr
 - Antigens, Viral, 77-5821
- Virus, Parvo
 - Temperature Sensitive Mutants, H-1 Virus, 77-5798
- Virus, Rous Sarcoma
 - DNA Repair, 77-5703
- Virus, SV40
 - DNA, Viral, 77-5791
 - Temperature Sensitive Mutants, 77-5795
 - Ultraviolet Rays, 77-5795

DNA, Viral

- Burkitt's Lymphoma
 - Virus, Epstein-Barr, 77-5826
- DNA Replication
 - DNA Polymerase, 77-5791
- RNA, Messenger
 - DNA-RNA Hybridization, 77-5834
- Virus, Adeno 2
 - DNA Replication, 77-5839
 - RNA, Messenger, 77-5804, 77-5830, 77-5834
 - Ultrastructural Study, 77-5829, 77-5837
- Virus, Adeno 3
 - Endonucleases, 77-5841
 - Transformation, Genetic, 77-5841
- Virus, Adeno 5
 - Ultrastructural Study, 77-5835
 - Virus Replication, 77-5836
- Virus, Adeno 7
 - Endonucleases, 77-5841
 - Transformation, Genetic, 77-5841
- Virus, Avian Leukosis-Sarcoma
 - DNA-RNA Hybridization, 77-5714
 - Nucleotides, Pheasant, 77-5714
- Virus, Avian Sarcoma
 - DNA-DNA Hybridization, 77-5712
 - Isolation and Characterization, 77-5712
- Virus, Bovine Adeno
 - Isolation and Characterization, 77-5723
- Virus, Epstein-Barr
 - Cell Transformation, Neoplastic, 77-5826
 - Isolation and Characterization, 77-5826
 - Ultrastructural Study, 77-5818
- Virus, Herpes Simplex 1
 - Isolation and Characterization, 77-5817
- Virus, Herpes Simplex 2, 77-5817
 - Isolation and Characterization, 77-5817
 - Thymidine Kinase, 77-5815
- Virus, Moloney Murine Sarcoma
 - Cell Transformation, Neoplastic, 77-5744
- Virus, Papilloma
 - Isolation and Characterization, 77-5845, 77-5846
- Virus, Polyoma
 - Cell Transformation, Neoplastic, 77-5760
 - Isolation and Characterization, 77-5761
 - Temperature Sensitive Mutants, 77-5760

DNA, Viral (cont'd)

- Virus, RNA Tumor
 - Reverse Transcriptase, 77-5709
- Virus, SV40
 - Antigenic Determinants, 77-5790
 - DNA Replication, 77-5791
 - DNA-RNA Hybridization, 77-5786
 - Histones, 77-5789
 - Isolation and Characterization, 77-5790, 77-5799
 - Ultrastructural Study, 77-5799, 77-5800
 - Viral Proteins, 77-5789
 - Virus Replication, 77-5800

Dodecylamine, *N,N*-Dimethyl-

- Nitrous Acid, Sodium Salt
- Carcinogenic Potential, Rat, 77-5602

Drosophila melanogaster

- Cyclophosphamide
 - Chromosome Aberrations, 77-5401
- Diethylamine, *N*-Nitroso-
 - Chromosome Aberrations, 77-5401
- Ethylene, Chloro-
 - Chromosome Aberrations, 77-5401
- Methanesulfonic Acid, Methyl Ester
 - Chromosome Aberrations, 77-5401
- Triazene, 3,3-Dimethyl-1-(*m*-pyridyl)-
 - Chromosome Aberrations, 77-5401

Duodenal Neoplasms

- Hydrazine, 1,1-Dimethyl-
- Corn Oil, 77-5502

Dyes

- Lung Neoplasms
 - Epidemiology, 77-5951
 - Occupational Hazard, 77-5951

Ear Neoplasms

- Hydrazine, 1,1-Dimethyl-
- Corn Oil, 77-5502

Elastin

- Smoking
 - Lung, 77-5594

Endometriosis

- Nephroblastoma
 - Case Report, 77-5913

Endometrium

- Carbenoxolone
- Mucosal Glycoproteins, Review, 77-5452

Endonucleases

- Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 - DNA, 77-5468
 - Endonucleases, 77-5468
- DNA
 - Endonucleases, 77-5468
- Methanesulfonic Acid, Methyl Ester
 - DNA Repair, 77-5990
- Virus, Adeno 3
 - DNA, Viral, 77-5841
- Virus, Adeno 7
 - DNA, Viral, 77-5841

Endoplasmic Reticulum

- Carcinogen, Chemical
- Mucosal Glycoproteins, Review, 77-5452

Environmental Hazard

- Carcinogen, Chemical

Environmental Hazard (cont'd)

- Risk Factor, Statistical Analysis, 77-5409

Ependymoma

- Virus, Papova, BK
 - Antigen-Antibody Reactions, 77-5843
 - Dosage Forms, 77-5843
 - Histological Study, Mouse, Hamster, 77-5843

Epoxide Hydratases

- Benzene, (Epoxyethyl)-
 - Enzymatic Activity, 77-5542
- Benzo(a)pyrene 4,5-Oxide
 - Enzymatic Activity, 77-5542
- Enzymatic Activity
 - Rat, 77-5542

Ergolines

- Mammary Neoplasms, Experimental
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-5577
 - Neoplasm Regression, 77-5577

Erythroleukemia

- Virus, C-Type RNA Tumor
 - Isolation and Characterization, 77-5733
- Virus, Friend Murine Leukemia
 - Isolation and Characterization, 77-5733

Escherichia coli

- Aflatoxin B1
 - Mutagenic Activity, 77-5511
- Aflatoxin G1
 - Mutagenic Activity, 77-5511
- DNA Repair
 - Lysogeny, 77-5677
- Ultraviolet Rays
 - DNA Repair, 77-5677

Esophageal Neoplasms

- Alcohol Drinking
 - Epidemiology, 77-5416, 77-5459
- Carcinogen, Environmental
 - Epidemiology, 77-5459
- Diet
 - Epidemiology, 77-5940
 - Epidemiology, Turkey, 77-5939
 - Tea, 77-5939
- Nitroso Compounds
 - Epidemiology, 77-5459
- Polycyclic Hydrocarbons
 - Epidemiology, 77-5459
- Smoking
 - Epidemiology, 77-5416, 77-5459
- Tars
 - Tea, 77-5939
- Tobacco
 - Epidemiology, 77-5459

Estra-1,3,5(10)-triene-3,17-diol(17 β)-, 3-Benzoate

- Vagina
 - Cytology, 77-5520

Estra-1,3,5(10)-triene-3,17 β -diol, 17-Pentanoate

- Vagina
 - Cytology, 77-5520

Estradiol

- Breast Neoplasms
 - Cell Survival, 77-5996
- DNA Repair
 - Virus, Herpes Simplex 2, 77-5814
- Mammary Neoplasms, Experimental

Estradiol (cont'd)

Benz(a)anthracene, 7,12-Dimethyl-, 77-5577

Cell Division, 77-5995

Hormones, 77-5996

Neoplasm Regression, 77-5577

Serum Albumin

Binding, 77-5519

Virus, Murine Mammary Tumor

Antigens, Viral, 77-5753

Estradiol Benzoate

see Estradiol, 1,3,5(10)-triene-3,17-diol(17 β)-, 3-Benzoate

Estradiol, 17-Ethynyl-

Liver Neoplasms

Epidemiology, 77-5525

Mestranol, 77-5525

Mammary Neoplasms, Experimental

Dog, 77-5526

Vagina

Cytology, 77-5520

Estragon Oil

Liver Regeneration

Rat, 77-5516

Estradiol

Vagina

Cytology, 77-5520

Ethrogens

Breast Neoplasms

Food Contamination, 77-5414

Cervix Neoplasms

Contraceptives, Oral, 77-5413

Uterine Neoplasms

Review, 77-5413

Vagina

Cytology, 77-5520

Ethane, Azoxy-

Salmonella typhimurium

Gastrointestinal System, Rat, 77-5473

Revertants, Germ-Free Rat, 77-5473

Ethane, 1,1-Dichloro-2,2-bis(p-chlorophenyl)-

Biphenyl

Hydroxylation, Microsomes, Liver, 77-5485

Ethane, 1,1,1-Trichloro-2,2-bis(p-chlorophenyl)-

Adipose Tissue

Metabolism, Review, 77-5495

Biphenyl

Hydroxylation, Microsomes, Liver, 77-5485

Cytochrome P-450

Dietary Proteins, 77-5492

Retinol, 77-5492

Neoplasms

Fish, 77-5958

Ethanol, 2-Amino-

Lipids

Cell Membrane, 77-5706

Ethanol, 2-Dimethylamino-

Lipids

Cell Membrane, 77-5706

Ethanol, 2-(Methylamino)-

Lipids

Cell Membrane, 77-5706

Ethionine

see Butyric Acid, 2-Amino-4-(ethylthio)-

Ethyl Alcohol

Cell Transformation, Neoplastic

Growth, 77-5782

Cells, Cultured

Growth, 77-5782

Gastric Mucosa

Glycoproteins, Review, 77-5451

Liver Cirrhosis

Epidemiology, 77-5943

Liver Neoplasms

Epidemiology, 77-5943

Mouth Neoplasms

Epidemiology, 77-5943

Ethylene, Chloro-

Adipose Tissue

Metabolism, Review, 77-5495

Angiosarcoma

Epidemiology, 77-5945

Chromosome Aberrations

Drosophila melanogaster, 77-5401

Epidemiology, 77-5496

Liver Neoplasms

Angiosarcoma, 77-5944

Neoplasms

Occupational Hazard, 77-5417

Ethylene, Chloro- Polymer

Breast Neoplasms

Epidemiology, 77-5946

Digestive System Neoplasms

Epidemiology, 77-5946

Intestinal Neoplasms

Epidemiology, 77-5946

Liver Neoplasms

Angiosarcoma, 77-5944

Neoplasms

Occupational Hazard, 77-5417

Occupational Hazard

Epidemiology, 77-5946

Urogenital Neoplasms

Epidemiology, 77-5946

Ethylene, 1,2-Dibromo-

DNA Repair

Rat, 77-5487

Ethylene, 1,1-Dichloro-2,2-bis(p-chlorophenyl)-

Biphenyl

Hydroxylation, Microsomes, Liver, 77-5485

Ethylene Oxide

Chromosome Aberrations

Rat, 77-5489

Salmonella typhimurium

Mutagenic Activity, 77-5489

Ethylene, Tetrachloro-

Adipose Tissue

Metabolism, Review, 77-5495

Liver Neoplasms

Carcinogenic Potential, 77-5408

Water Pollutants

Carcinogenic Potential, 77-5408

Ethylene Thiourea

see 1-Imidazolidinethione

- Ethylene, Trichloro-**
Adipose Tissue
Metabolism, Review, 77-5495
Salmonella typhimurium
Mutagenic Activity, 77-5488
- Ethylenethiourea**
see 2-Imidazolidinethione
- Ethynerone**
Mammary Neoplasms, Experimental
Adenocarcinoma, 77-5521
Adenoma, 77-5521, 77-5527
Dog, 77-5521
Monkey, 77-5521
- Exonucleases**
DNA Polymerase
Enzymatic Activity, 77-5535
Nucleotides
Enzymatic Activity, 77-5535
Purine-6-thiol
Enzymatic Activity, 77-5535
- Fatty Acids**
Aflatoxin B1
Co-carcinogenic Effect, Fish, 77-5406
Breast Neoplasms
Risk Factor, Review, 77-5461
Hepatosoma
Fish, Review, 77-5406
Intestinal Neoplasms
Risk Factor, Review, 77-5461
Mammary Neoplasms, Experimental
Hormone Dependence, 77-5999
- Fennel Oil**
Liver Regeneration
Rat, 77-5516
- Fetal Globulins**
Liver Neoplasms
Review, 77-5427
- Fibrinolysis**
Benzo(a)pyrene
Cell Transformation, Neoplastic, 77-5556
Cells, Cultured, 77-5556
Urea, Ethyl Nitroso-
Cells, Cultured, 77-5612
- Fibroadenoma**
see Adenofibroma
- Fibroblasts**
Cytochalasin B
Cell Division, 77-5973
Cell Survival, 77-5973
Fibrosarcoma
Ultrastructural Study, 77-5925
- Fibrosarcoma**
Antigens, Neoplasm
Cells, Cultured, 77-5881
Culture Media, 77-5881
Isolation and Characterization, 77-5882
Asbestos
Rat, 77-5644
Fibroblasts
Ultrastructural Study, 77-5925
Fish
Histological Study, 77-5958
- Fibrosarcoma (cont'd)**
Genetics
Immune Response, 77-5887
Histiocytes
Ultrastructural Study, 77-5925
Pesticides
Fish, 77-5958
Skin Neoplasms
Case Report, 77-5926
Ultrastructural Study, 77-5926
Ultraviolet Rays
Immune Response, 77-5856
Virus, Kirsten Murine Sarcoma
Cells, Cultured, 77-5749
- Fibroxsanthoma, Malignant**
see Fibrosarcoma
- Fluclorolone Acetonide**
DNA Replication
Mouse, 77-5540
Skin Neoplasms
Carcinoma, 77-5540
Papilloma, 77-5540
- Fluocinolone Acetonide**
DNA Replication
Mouse, 77-5540
Skin Neoplasms
Carcinoma, 77-5540
Papilloma, 77-5540
- Fluoranthene**
Deuterium
Synthesis, 77-5567
- 9H-Fluorene, 2-Nitro-**
Salmonella typhimurium
Gastrointestinal System, Rat, 77-5473
Revertants, Germ-Free Rat, 77-5473
- Folic Acid**
Acetamide, *N*-Fluoren-2-yl-
Acetamide, *N*-(5-Hydroxyfluoren-2-yl)-, 77-5466
- Food Contamination**
Aflatoxin B1
Chromatographic Analysis, 77-5513
Aflatoxin M1
Chromatographic Analysis, 77-5513
Breast Neoplasms
Estrogens, 77-5414
Mycotoxins, 77-5414
Patulin
Isolation and Characterization, 77-5514
- Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-**
Bladder Neoplasms
Rat, 77-5464
Ultrastructural Study, 77-5464
- Freund's Adjuvant**
Lymphosarcoma
Immune Response, 77-5867
Immunologic Technics, 77-5867
- 2-Furaldehyde, 5-Nitro-, Semicarbazone**
Cells, Cultured
Metabolism, 77-5625
- Galactosamine**
Colonic Neoplasms
Glycoproteins, Review, 77-5450

Gallic Acid, Propyl Ester

- Dimethylamine, *N*-Nitroso-
Rat, 77-5610

Gangrene

- Arsenic
Epidemiology, Taiwan, 77-5638

Gastric Mucosa

- Benzoic Acid, 2-(Acetyloxy)-
Glycoproteins, Review, 77-5451
- Ethyl Alcohol
Glycoproteins, Review, 77-5451
- Gastrointestinal Neoplasms
Glycoproteins, Review, 77-5451
- Indole-3-acetic Acid, 1-(*p*-Chlorobenzoyl)-4-methoxy-2-
methyl-
Glycoproteins, Review, 77-5451
- 3,5-Pyrazolidinedione, 4-Butyl-1,2-diphenyl-
Glycoproteins, Review, 77-5451
- Stress
Glycoproteins, Review, 77-5451

Gastrointestinal Neoplasms

- Gastric Mucosa
Glycoproteins, Review, 77-5451
- Genetics
Epidemiology, 77-5443
- Precancerous Conditions
Glycoproteins, Review, 77-5451

Gastrointestinal System

- Carbenoxolone
Cervix Uteri, 77-5452

Genetics

- Brain Neoplasms
Astrocytoma, 77-5901
Breast Neoplasms, 77-5442
Sarcoma, 77-5442
- Breast Neoplasms
Case Report, 77-5689
Epidemiology, 77-5443
- Carcinoid Tumor
Review, 77-5447
- Colonic Neoplasms
Epidemiology, 77-5904
- Fibrosarcoma
Immune Response, 77-5887
- Gastrointestinal Neoplasms
Epidemiology, 77-5443
- Glomangioma
Review, 77-5439
- Hamartoma
Review, 77-5448
- Histocompatibility Antigens
Immune Response, 77-5887
- Hodgkin's Disease
Histocompatibility Antigens, 77-5897
- Leukemia
Epidemiology, 77-5443
- Leukemia, Myeloblastic
Chromosome Aberrations, 77-5441
- Lymphoma
Immune Response, 77-5887
- Mammary Neoplasms, Experimental
Virus, Murine Mammary Tumor, 77-5752
- Melanoma
Review, 77-5447
- Multiple Myeloma

Genetics (cont'd)

- Antibody Formation, 77-5875
- Blood Proteins, 77-5875
- Immunoglobulins, 77-5875
- Nasopharyngeal Neoplasms
Epidemiology, 77-5935
- Neoplasms
Breast Neoplasms, 77-5442
Epidemiology, 77-5441, 77-5442, 77-5456, 77-5904
Immune Response, 77-5441
Review, 77-5436
Sarcoma, 77-5442
- Neoplasms, Multiple Primary
Breast Neoplasms, 77-5442
Case Report, 77-5903
Epidemiology, 77-5442
Hamartoma, 77-5903
Sarcoma, 77-5442
- Neuroblastoma
Review, 77-5447
- Paraganglioma, Nonchromaffin
Review, 77-5439, 77-5447
- Pheochromocytoma
Review, 77-5447
- Thyroid Neoplasms
Review, 77-5447
- Urogenital Neoplasms
Carcinoma, Transitional Cell, 77-5936
Case Report, 77-5936
Kidney Diseases, 77-5936
Neoplasms, Multiple Primary, 77-5936
- Uterine Neoplasms
Epidemiology, 77-5904
- Virus, Murine Mammary Tumor
Epidemiology, 77-5429
- Virus, Radiation Leukemia
Histocompatibility Antigens, 77-5736, 77-5737
- Giant Cell Tumors
Pancreatic Neoplasms
Histological Study, 77-5923
Ultrastructural Study, 77-5923
- Glioblastoma Multiforme
Brain Neoplasms
Guanyl Cyclase, 77-5993
Cholanthrene, 3-Methyl-
Mouse, 77-5766
Urea, Ethyl Nitroso-
Histological Study, 77-5615
Virus, C-Type RNA Tumor
Ultrastructural Study, 77-5766
- Glioma
Dexamethasone
Contact Inhibition, 77-5987
DNA Replication, 77-5987
Urea, Ethyl Nitroso-
Brain Neoplasms, 77-5613
Histological Study, 77-5615
- Globin
RNA, Messenger
DNA-RNA Hybridization, 77-5734
- Glomangioma
Genetics
Review, 77-5439

- Glucosaminidase**
 Sarcoma
 Benz(a)anthracene, 7,12-Dimethyl-, 77-5573
 Cells, Cultured, 77-5573
 Virus, Rous Sarcoma, 77-5573
- Glucose, 2-Deoxy-**
 Cell Membrane
 Metabolism, 77-5618
 Cell Transformation, Neoplastic
 Metabolism, 77-5618
 Temperature Sensitive Mutants, 77-5618
 Lactic Acid
 Cell Transformation, Neoplastic, 77-5618
- Glucuronidase**
 Acetamide, *N*-Fluoren-2-yl-
 Carcinogenic Metabolite, 77-5472
 DNA, Binding, 77-5472
 Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 Carcinogenic Metabolite, 77-5472
 DNA, Binding, 77-5472
 Benzo(a)pyrene, 4,5-Dihydro-4,5-dihydroxy-
 Metabolism, Hamster, 77-5563
 Bladder Neoplasms
 Microsomes, Liver, 77-5472
 Hydroxylamine, *N*-4-Biphenyl-
 Carcinogenic Metabolite, 77-5472
 DNA, Binding, 77-5472
 Hydroxylamine, *N*-1-Naphthyl-
 Carcinogenic Metabolite, 77-5472
 DNA, Binding, 77-5472
 Hydroxylamine, *N*-2-Naphthyl-
 Carcinogenic Metabolite, 77-5472
 DNA, Binding, 77-5472
 Hydroxylamine, *N*-(*p*-Phenylazo)phenyl-
 Carcinogenic Metabolite, 77-5472
 DNA, Binding, 77-5472
 Smoking
 Lung, 77-5594
- Glutamine**
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 Mutagenic Activity, 77-5622
 Temperature Sensitive Mutants, 77-5622
 Virus, SV40
 Mutagenic Activity, 77-5622
 Temperature Sensitive Mutants, 77-5622
- Glutathione**
 Acetamide, *N*-Fluoren-2-yl-
 Liver, Rat, 77-5466
 Retronecine, 3,8-Didehydro-
 Binding, 77-5505
- Glycogenesis**
 Hepatoma
 Urea, Ethyl Nitroso-, 77-5614
 Urea, Ethyl Nitroso-
 Transplacental Carcinogenesis, 77-5614
- Glycoproteins**
 Bladder Neoplasms
 Isolation and Characterization, 77-5889
 Cell Membrane
 Isolation and Characterization, 77-5969, 77-5980
 77-5981
 Cell Transformation, Neoplastic
 Cell Membrane, 77-5969
 Colonic Neoplasms
- Glycoproteins (cont'd)**
 Isolation and Characterization, 77-5889
 Liver Neoplasms
 Cell Membrane, 77-5981
 Mammary Neoplasms, Experimental
 Cell Membrane, 77-5980
 Virus, Friend Murine Leukemia
 Cell Transformation, Neoplastic, 77-5767
- Glycoside Hydrolases**
 Methanesulfonic Acid, Methyl Ester
 DNA Repair, 77-5990
- Gonadoblastoma**
 see Disgerminoma
- Gonadotropins, Chorionic**
 Choriocarcinoma
 Cells, Cultured, 77-5970
- Granular Cell Tumor, Malignant**
 see Sarcoma
- Granulocytes**
 Cell Differentiation
 Cells, Cultured, 77-5963
- Growth**
 Multiple Myeloma
 IgG, 77-5962
- Growth Substances**
 Bactopeptone
 Cells, Cultured, 77-5966
 Benzo(a)pyrene
 Cell-Cycle Kinetics, 77-5968
 Phosphoinositides, 77-5968
 Breast Neoplasms
 Cell Division, 77-5971
 Cell Transformation, Neoplastic
 Cell Adhesion, 77-5972
 HeLa Cells
 Alkaline Phosphatase, 77-5994
 Virus, SV40
 Cell-Cycle Kinetics, 77-5968
 Phosphoinositides, 77-5968
- Guanidine, Methyl-**
 Nitrous Acid, Sodium Salt
 Carcinogenic Potential, Rat, 77-5602
- Guanidine, 1-Methyl-3-nitro-1-nitroso-**
 Cell Transformation, Neoplastic
 Karyotyping, 77-5630
 Cells, Cultured
 Chromosome Aberrations, 77-5631
 Mutagenic Activity, 77-5536, 77-5537, 77-5580
 77-5680, 77-5681
- DNA**
 Mitochondria, 77-5623
- Glutamine**
 Mutagenic Activity, 77-5622
 Temperature Sensitive Mutants, 77-5622
- Hyperplasia**
 Prostate, Rat, 77-5620
- Retinoic Acid**
 Hyperplasia, 77-5620
- Retinol Acetate**
 Hyperplasia, 77-5620
- Retinyl Methyl Ether**
 Hyperplasia, 77-5620
- Virus, Moloney Murine Sarcoma-Leukemia**

Guanidine, 1-Methyl-3-nitro-1-nitroso- (cont'd)
Temperature Sensitive Mutants, 77-5743

Guanosine Cyclic 3',5' Monophosphate
Hepatoma
Butyric Acid, 2-Amino-4-(ethylthio)-, 77-5499
Virus, Moloney Murine Sarcoma
Neoplasms, Experimental, 77-5746

Guanyl Cyclase
Brain Neoplasms
Enzymatic Activity, 77-5993
Glioblastoma Multiforme, 77-5993
Meningioma, 77-5993
Neurinoma, 77-5993
Oligodendroglioma, 77-5993
Hepatoma
Butyric Acid, 2-Amino-4-(ethylthio)-, 77-5499

Gynecologic Neoplasms
Occupational Hazard
Epidemiology, 77-5951
4,4'-Stilbenediol, α,α' -Diethyl-
Histological Study, 77-5518

Hamartoma
Breast Neoplasms
Carcinoma, 77-5439
Genetics
Review, 77-5448
Neoplasms, Multiple Primary
Genetics, 77-5903
Nephroblastoma
Epidemiology, 77-5444
Thyroid Neoplasms
Adenocarcinoma, 77-5439

Head and Neck Neoplasms
Lipomatosis
Review, 77-5439

Heart Neoplasms
Mesothelioma
Ultrastructural Study, 77-5924

Heat
DNA
Binding, Acridine, 77-5676
Epidermal Cells, 77-5676
Ultraviolet Rays
DNA Denaturation, Synergistic Effect, 77-5676

HeLa Cells
Cell Adhesion
Agar, 77-5974
Growth Substances
Alkaline Phosphatase, 77-5994
Karyotyping
Cell Line, 77-5908
Pentadecan-2-one
Cell Adhesion, 77-5974
RNA
Ultraviolet Rays, 77-5838
RNA, Messenger
Ultraviolet Rays, 77-5838
RNA, Viral
Ultraviolet Rays, 77-5838
Virus, Adeno 2
DNA Nucleotidyltransferases, 77-5840
Virus, Adeno 2 - SV40 Hybrid
Antigens, Viral, 77-5802

HeLa Cells (cont'd)
Virus, SV40
Antigens, Viral, 77-5802

Hemagglutinins, Viral
Virus, Parvo
Temperature Sensitive Mutants, H-1 Virus, 77-5798

Hemangioendothelioma
Benzene, Hexachloro-
Hamster, 77-5483
Liver Neoplasms, 77-5483
Splenic Neoplasms, 77-5483
Liver Neoplasms
Arsenic, 77-5637
Hydrazine, 1,2-Dimethyl-, 77-5500
Phosphoric Acid, Titanium Salt
Hamster, 77-5644
Radiation, Ionizing
Mouse, 77-5655

Hemangioma
Ovarian Neoplasms
Hydrazine, 1,2-Dimethyl-, 77-5500

Hemangiosarcoma
see Angiosarcoma

Hematopoietic Stem Cells
Hydrazine, Phenyl-
Mouse, 77-5964
Leukemia, Myelocytic
Review, 77-5446
Polycythemia Vera
Review, 77-5446

Hepatoma
Aflatoxin B1
Aroclor 1254, 77-5506
Fish, Review, 77-5406
Androsta-1,4-dien-3-one, 17 β -Hydroxy-17-methyl-
Case Report, 77-5921
Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
Lecithins, 77-5481
Benzene, Hexachloro-
Hamster, 77-5483
Butyric Acid, 2-Amino-4-(ethylthio)-
Choline, Chloride, Carbamate, 77-5499
Guanosine Cyclic 3',5' Monophosphate, 77-5499
Guanyl Cyclase, 77-5499
Phosphodiesterases, 77-5499
Xanthine, 3-Isobutyl-1-methyl-, 77-5499
Diethylamine, *N*-Nitroso-
Acetamide, *N*-Fluoren-2-yl-, 77-5920
Ultrastructural Study, Monkey, 77-5608
Virus, Hepatitis, 77-5608
Fatty Acids
Fish, Review, 77-5406
Heptachlor
Neoplasm Metastasis, 77-5490
Heptachlor Epoxide
Neoplasm Metastasis, 77-5490
Lecithins
Isolation and Characterization, 77-5481
Precancerous Conditions
Animal Model, Rat, 77-5920
Urea, Ethyl Nitroso-
Glycogenosis, 77-5614
Precancerous Conditions, 77-5614
Transplacental Carcinogenesis, 77-5614

- Hepatoma (cont'd)**
 Virus, Hepatitis
 Ultrastructural Study, Monkey, 77-5608
- Heptachlor**
 Hepatoma
 Neoplasm Metastasis, 77-5490
- Heptachlor Epoxide**
 Hepatoma
 Neoplasm Metastasis, 77-5490
- Hereditary Diseases**
 Neoplasms
 Inbreeding, Review, 77-5437
- Hexamethylenetetramine**
 Nitrous Acid, Sodium Salt
 Carcinogenic Potential, Rat, 77-5602
- l-Hexanamine, N-Hexyl-N-nitroso-**
 Nitrous Acid
Saccharomycopsis lipolytica, 77-5604
- Hexosamines**
 Smoking
 Lung, 77-5594
- Histiocytes**
 Fibrosarcoma
 Ultrastructural Study, 77-5925
- Histocompatibility Antigens**
 Genetics
 Immune Response, 77-5887
 Hodgkin's Disease
 Epidemiology, 77-5897
 Genetics, 77-5897
 T-Lymphocytes
 Immune Response, 77-5750
 Lymphoma
 Immune Response, 77-5750
 T-Lymphocytes, 77-5750
 Nasopharyngeal Neoplasms
 Epidemiology, 77-5935
 Retinoblastoma
 Epidemiology, 77-5879
 Sarcoma
 Virus, SV40, 77-5885
 Sarcoma, Yoshida
 Immune Response, 77-5876
 Virus, Radiation Leukemia
 Genetics, 77-5736, 77-5737
 Virus, SV40
 Detergents, 77-5885
 Isolation and Characterization, 77-5885
- Histones**
 Leukemia
 Cells, Cultured, 77-5730
 Isolation and Characterization, 77-5730
 Mouse, 77-5857
 Lymphosarcoma
 Mouse, 77-5857
 Virus, SV40
 DNA, Viral, 77-5789
- Hodgkin's Disease**
 Antigens, Heterogenetic
 Antigen-Antibody Reactions, 77-5739
 Histocompatibility Antigens
 Epidemiology, 77-5897
- Hodgkin's Disease (cont'd)**
 Genetics, 77-5897
 Immune Serums
 Antibodies, Viral, 77-5739
 Occupational Hazard
 Epidemiology, 77-5948
 Virus, Gross Murine Leukemia
 Antibodies, Viral, 77-5739
- Hormones**
 Digestive System Neoplasms
 Review, 77-5415
 Mammary Neoplasms, Experimental
 Benz(a)anthracene, 7,12-Dimethyl-, 77-5996
 Estradiol, 77-5996
 Pregnancy, 77-5995
 Prolactin, 77-5996
- Hybrid Cells**
 Cell Transformation, Neoplastic
 Methods, 77-5428
- Hycanthone**
 Cell Transformation, Neoplastic
 Carcinogenic Potential, 77-5534
 Virus, Rauscher Murine Leukemia
 Cell Transformation, Neoplastic, 77-5534
- Hydatidiform Mole**
 Nitric Acid
 Water Pollutants, 77-5598
- Hydrazine**
 Uncoupling Agents
 Oxidative Phosphorylation, 77-5504
- Hydrazine, 1,1-Dimethyl-**
 Colonic Neoplasms
 Cereals, 77-5502
 Corn Oil, 77-5502
 Dietary Fats, 77-5502
 Histological Study, Rat, 77-5502
 Duodenal Neoplasms
 Corn Oil, 77-5502
 Ear Neoplasms
 Corn Oil, 77-5502
- Hydrazine, 1,2-Dimethyl-**
 DNA
 Alkylation, Rat, 77-5503
 Purine, 2-Amino-6-methoxy-, 77-5503
 Intestinal Neoplasms
 Adenoma, 77-5500
 Carcinoma, 77-5500
 Phosphonic Acid, (2,2,2-Trichloro-1-hydroxyethyl)-
 Dimethyl Ester, 77-5500
 Sarcoma, Reticulum Cell, 77-5500
 Liver Neoplasms
 Hemangioendothelioma, 77-5500
 Phosphonic Acid, (2,2,2-Trichloro-1-hydroxyethyl)-
 Dimethyl Ester, 77-5500
 Ovarian Neoplasms
 Hemangioma, 77-5500
 Phosphonic Acid, (2,2,2-Trichloro-1-hydroxyethyl)-
 Dimethyl Ester, 77-5500
 Uncoupling Agents
 Oxidative Phosphorylation, 77-5504
 Uterine Neoplasms
 Phosphonic Acid, (2,2,2-Trichloro-1-hydroxyethyl)-
 Dimethyl Ester, 77-5500
 Sarcoma, 77-5500

Hydrazine, 1,2-Dimethyl-, Dihydrochloride

- Colonic Neoplasms
- Carcinoma, 77-5501
- Cell Cycle Kinetics, 77-5501

Hydrazine, Phenyl-

- Hematopoietic Stem Cells
- Mouse, 77-5964

Hydro-Lyases

- Benz(a)anthracene, 5,6-Dihydro-5,6-epoxy-
Liver, 77-5543
- Benzo(a)pyrene 4,5-Oxide
Liver, 77-5543
- Benzo(a)pyrene 7,8-Oxide
Liver, 77-5543
- Benzo(a)pyrene 11,12-Oxide
Liver, 77-5543
- Cholanthrene, 11,12-Dihydro-11,12-epoxy-3-methyl-
Liver, 77-5543
- Dibenz(a,h)anthracene, 5,6-Dihydro-5,6-epoxy-
liver, 77-5543
- Naphthalene 1,2-Oxide
Liver, 77-5543
- Octene 1,2-Oxide
Liver, 77-5543
- Phenanthrene, 9,10-Dihydro-9,10-epoxy-
Liver, 77-5543
- Phenanthrene, 9,10-Epoxy-9,10-dihydro-
Liver, 77-5543

Hydroquinone, α -Butyl-

- Dimethylamine, *N*-Nitroso-
Rat, 77-5610

Hydroxylamine, *N*-4-Biphenyl-

- Glucuronidase
- Carcinogenic Metabolite, 77-5472
- DNA, Binding, 77-5472
- Microsomes, Liver
- Carcinogenic Metabolite, 77-5472

Hydroxylamine, *N*-1-Naphthyl-

- Glucuronidase
- Carcinogenic Metabolite, 77-5472
- DNA, Binding, 77-5472
- Microsomes, Liver
- Carcinogenic Metabolite, 77-5472

Hydroxylamine, *N*-2-Naphthyl-

- Glucuronidase
- Carcinogenic Metabolite, 77-5472
- DNA, Binding, 77-5472
- Microsomes, Liver
- Carcinogenic Metabolite, 77-5472

Hydroxylamine, *N*-(*p*-Phenylazo)phenyl-

- Glucuronidase
- Carcinogenic Metabolite, 77-5472
- DNA, Binding, 77-5472
- Microsomes, Liver
- Carcinogenic Metabolite, 77-5472

Hydroxylases

- Acetamide, *N*-Fluoren-2-yl-
Liver, Rat, 77-5466
- Antipyrine
Liver, 77-5569
- Barbituric Acid, 5-(1-Cyclohexen-1-yl)-1,5-dimethyl-
Liver, 77-5569
- Benzo(a)pyrene

Hydroxylases (cont'd)

- Liver, 77-5569
- Coumarin
Liver, 77-5569
- Liver, 77-5569

Hydroxysteroid Dehydrogenases

- Aflatoxin B1
Aflatoxicol, 77-5507

Hyperplasia

- Bladder
F12 Medium, 77-5977
- Organ Culture, 77-5977
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
Prostate, Rat, 77-5620
- Retinoic Acid, 77-5620
- Retinol Acetate, 77-5620
- Retinyl Methyl Ether, 77-5620

Hysterectomy

- Cervix Neoplasms
- Epidemiology, 77-5928

ICR 191

- Cells, Cultured
- Mutagenic Activity, 77-5680, 77-5681

IgG

- Multiple Myeloma
Growth, 77-5962
- Virus, Papilloma
Antibody Formation, 77-5870

IgM

- Virus, Papilloma
Antibody Formation, 77-5870

Immune Serums

- Hodgkin's Disease
Antibodies, Viral, 77-5739
- Leukemia
Antibodies, Viral, 77-5739
- Leukemia, Lymphocytic
Cell Differentiation, 77-5740
- Colony-Stimulating Activity, 77-5740
- Virus, Murine Leukemia, 77-5740
- Virus, Moloney Murine Leukemia
Cell Transformation, Neoplastic, 77-5860
- Virus Replication, 77-5860

Immunity

- Liver Neoplasms
Acetamide, *N*-Fluoren-2-yl-, 77-5427
- Aniline, *N,N*-Dimethyl-*p*-phenylazo-, 77-5427
- Diethylamine, *N*-Nitroso-, 77-5427
- Review, 77-5427

Immunity, Cellular

- Virus, Marek's Disease Herpes
Antigens, Neoplasm, 77-5880
- Chicken, 77-5880
- Virus, Moloney Murine Leukemia
Virus, Moloney Murine Sarcoma, 77-5745
- Virus, Radiation Leukemia
T-Lymphocytes, 77-5871
- Macrophages, 77-5871

Immunoglobulins

- Multiple Myeloma
Genetics, 77-5875
- RNA, Messenger

- Immunoglobulins (cont'd)**
 - DNA-RNA Hybridization, 77-5989
- Immunologic Deficiency Syndromes**
 - Leukemia
 - Ataxia Telangiectasia, 77-5434
 - Lymphoma
 - Ataxia Telangiectasia, 77-5434
- Immunologic Technics**
 - Lymphosarcoma
 - Freund's Adjuvant, 77-5867
 - Sarcoma
 - Carcinoembryonic Antigen, 77-5869
 - Cholanthrene, 3-Methyl-, 77-5869
- Immunosuppression**
 - Sarcoma, Mast Cell
 - Cells, Cultured, 77-5861
 - Ultraviolet Rays
 - Carcinogenic Activity, Review, 77-5421
 - Virus, Moloney Murine Leukemia
 - Spleen, 77-5860
 - Virus, Moloney Murine Sarcoma, 77-5745
- Indole-3-acetic Acid, 1-(*p*-Chlorobenzoyl)-4-methoxy-2-methyl-**
 - Gastric Mucosa
 - Glycoproteins, Review, 77-5451
- Insulin**
 - Virus, SV40
 - Cell Transformation, Neoplastic, 77-5788
- Interferon**
 - Radiation, Ionizing
 - Cell Division, 77-5684
 - Cell Transformation, Neoplastic, 77-5684
- Intestinal Neoplasms**
 - Acetic Acid, Methylnitrosaminomethyl Ester
 - Dose-Response Study, Rat, 77-5611
 - Asbestos
 - Epidemiology, 77-5955
 - Dimethylamine, *N*-Nitroso-
 - Dose-Response Study, Rat, 77-5611
 - Ethylene, Chloro- Polymer
 - Epidemiology, 77-5946
 - Fatty Acids
 - Risk Factor, Review, 77-5461
 - Hydrazine, 1,2-Dimethyl-
 - Adenoma, 77-5500
 - Carcinoma, 77-5500
 - Phosphonic Acid, (2,2,2-Trichloro-1-hydroxyethyl)-
 - Dimethyl Ester, 77-5500
 - Sarcoma, Reticulum Cell, 77-5500
 - Methane, Azoxy-
 - Candididin, 77-5474
 - Cholestyramine, 77-5474
 - Occupational Hazard
 - Epidemiology, 77-5946
- Intestine, Small**
 - Cell Cycle Kinetics
 - Review, 77-5961
- Isoantigens**
 - Colonic Neoplasms
 - Glycoproteins, Review, 77-5450
- Jaundice, Obstructive**
 - Pancreatic Neoplasms
 - Epidemiology, Review, 77-5449
- Karyotyping**
 - Benz(a)anthracene, 7,12-Dimethyl-
 - Cell Transformation, Neoplastic, 77-5630
 - Benzo(a)pyrene
 - Cell Transformation, Neoplastic, 77-5630
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Cell Transformation, Neoplastic, 77-5630
 - HeLa Cells
 - Cell Line, 77-5908
 - Leukemia
 - Chromosome Abnormalities, 77-5900
 - Neoplasms
 - Cell Line, 77-5906
 - Virus, SV40
 - Cell Transformation, Neoplastic, 77-5783
- Kidney**
 - Aroclor 1254
 - Metabolism, Trout, 77-5506
 - Ochratoxin A
 - Rat, 77-5515
- Kidney Diseases**
 - Urogenital Neoplasms
 - Genetics, 77-5936
- Kidney Neoplasms**
 - Acetic Acid, Methylnitrosaminomethyl Ester
 - Dose-Response Study, Rat, 77-5611
 - Aryl Hydrocarbon Hydroxylases
 - Smoking, 77-5589
 - Asbestos
 - Epidemiology, 77-5955
 - Carcinoma
 - Aryl Hydrocarbon Hydroxylases, 77-5589
 - Case Report, 77-5690
 - Radiation, Ionizing, 77-5690
 - Dimethylamine, *N*-Nitroso-
 - Ascorbic Acid, 77-5599
 - Dose-Response Study, Rat, 77-5611
 - Rat, 77-5599
 - Nitrous Acid, Sodium Salt
 - Rat, 77-5599
- Lactate Dehydrogenase**
 - Lung Neoplasms
 - Enzymatic Activity, 77-5656
- Lactic Acid**
 - Glucose, 2-Deoxy-
 - Cell Transformation, Neoplastic, 77-5618
- Laryngeal Neoplasms**
 - Smoking
 - Epidemiology, 77-5416
- Lead**
 - Aging
 - Immune Response, 77-5873
 - Mouse, 77-5873
 - DNA Replication
 - Carcinogenic Activity, 77-5634
 - Mutagenic Activity, 77-5634
 - Mouse
 - Immune Response, 77-5873
 - Neoplasms, Experimental
 - Trace Elements, Review, 77-5412
- Lecithins**
 - Hepatoma
 - Benzenamine, *N,N*-Dimethyl-4-((3-

Lecithins (cont'd)

- methylphenylazo)-, 77-5481
- Isolation and Characterization, 77-5481

Leiomyoma

- Leiomyosarcoma
 - Review, 77-5439
- Uterine Neoplasms
 - Histological Study, 77-5912
 - Ultrastructural Study, 77-5912

Leiomyosarcoma

- Leiomyoma
 - Review, 77-5439

Leukemia

- Anemia, Aplastic
 - Statistical Analysis, 77-5440
- Antigens, Heterogenetic
 - Antigen-Antibody Reactions, 77-5739
- Ataxia Telangiectasia
 - Immunologic Deficiency Syndromes, 77-5434
- Benz(a)anthracene, 7,12-Dimethyl-
 - Virus, C-Type RNA Tumor, 77-5765
 - Virus Replication, 77-5765
- Bone Marrow Cells
 - Reverse Transcriptase, 77-5849
- C.I. Direct Violet 100
 - Rat, 77-5478
- Cell Membrane
 - Lipids, 77-5998
- Cells, Cultured
 - Histones, 77-5730
- Chromosome Aberrations
 - Epidemiology, 77-5444
 - Review, 77-5435
- Chromosome Abnormalities
 - Karyotyping, 77-5900
- Genetics
 - Epidemiology, 77-5443
- Histones
 - Isolation and Characterization, 77-5730
 - Mouse, 77-5857
- Immune Serums
 - Antibodies, Viral, 77-5739
- B-Lymphocytes
 - Cell Membrane, 77-5663
- T-Lymphocytes
 - Cell Membrane, 77-5663
- Occupational Hazard
 - Epidemiology, 77-5948
- Ovarian Neoplasms
 - Statistical Analysis, 77-5440
- Radiation, Ionizing
 - Epidemiology, 77-5682
 - B-Lymphocytes, 77-5663
 - T-Lymphocytes, 77-5663
 - Mouse, 77-5655
 - Mutagenic Activity, 77-5649
- Virus, Gross Murine Leukemia
 - Antibodies, Viral, 77-5739
- Virus, Leukemia
 - Bone Marrow Cells, 77-5849
 - Isolation and Characterization, 77-5849
- Virus, Rauscher Murine Leukemia
 - Mouse, 77-5857

Leukemia, Acute Granulocytic
see Leukemia, Myeloblastic**Leukemia, Lymphoblastic**

- Antibodies, Neoplasm
 - Immune Response, 77-5891
- Antigen-Antibody Reactions
 - Antigens, Neoplasm, 77-5878
 - Cell Line, 77-5878
- Cell Line
 - Null Cells, 77-5896
- Chromosome Aberrations
 - Epidemiology, 77-5899
 - Review, 77-5431
- Chromosome Abnormalities
 - Case Report, 77-5898
- Ethnic Groups
 - Epidemiology, 77-5458
- Urea, 1-Butyl-1-nitroso-
 - Mouse, 77-5617
- Urea, Methyl Nitroso-
 - Mouse, 77-5617
- Virus, Epstein-Barr
 - DNA-DNA Hybridization, 77-5896
 - Receptors, Viral, 77-5878
- Virus, Gross Murine Leukemia
 - Antibodies, Viral, 77-5739

Leukemia, Lymphocytic

- Adenyl Cyclase
 - Enzymatic Activity, 77-5997
- Antibody Formation
 - Neoplasm Regression, Spontaneous, 77-5731
- Immune Serums
 - Cell Differentiation, 77-5740
 - Colony-Stimulating Activity, 77-5740
- Lymphocytes
 - Adenyl Cyclase, 77-5997
 - Receptors, Hormone, 77-5997
- B-Lymphocytes
 - Review, 77-5446
- Neoplasms, Radiation-Induced
 - Fetus, 77-5683
- Virus, Friend Murine Leukemia
 - Neoplasm Regression, Spontaneous, 77-5731
- Virus, Helper
 - Neoplasm Regression, Spontaneous, 77-5731
- Virus, Murine Leukemia
 - Bone Marrow Cells, 77-5740
 - Immune Serums, 77-5740
 - Leukocytes, 77-5740

Leukemia, Myeloblastic

- Benz(a)anthracene, 7,12-Dimethyl-
 - Chromosomes, 77-5575
 - Cytochemical Study, 77-5575
 - DNA, 77-5575
 - Ultrastructural Study, 77-5575
- Chromosome Aberrations
 - Review, 77-5431
- Genetics
 - Chromosome Aberrations, 77-5441
- Virus, Gross Murine Leukemia
 - Antibodies, Viral, 77-5739

Leukemia, Myelocytic

- Chromosome Aberrations
 - Review, 77-5431
- Hematopoietic Stem Cells

Leukemia, Myelocytic (cont'd)

Review, 77-5446

Liver

Neoplasm Metastasis, 77-5895

Neoplasm Metastasis

Ultrastructural Study, 77-5895

Transplantation, Heterologous

Chromosomes, Human, 21-22, 77-5858

Histological Study, 77-5858

Mouse, Nude, 77-5858

Transplantation, Homologous

Neoplasm Metastasis, 77-5895

Leukemia, Myelomonocytic

see Leukemia, Myelocytic

Leukocytes

Leukemia, Lymphocytic

Virus, Murine Leukemia, 77-5740

Leupeptins

Bladder Neoplasms

1-Butanol, 4-(Butylnitrosamino)-, 77-5606

Ultrastructural Study, Rat, 77-5606

Leydig Cell Tumor

Testicular Neoplasms

Radiation, Ionizing, 77-5685

Lipids

1-Butanol, 2-Amino-

Cell Membrane, 77-5706

Cell Membrane

Cells, Cultured, 77-5706

Cells, Cultured

Histological Study, 77-5706

Choline

Cell Membrane, 77-5706

Ethanol, 2-Amino-

Cell Membrane, 77-5706

Ethanol, 2-Dimethylamino-

Cell Membrane, 77-5706

Ethanol, 2-(Methylamino)-

Cell Membrane, 77-5706

Leukemia

Cell Membrane, 77-5998

Mammary Neoplasms, Experimental

Hormone Dependence, 77-5999

Sebaceous Gland Neoplasms

Cell Differentiation, 77-5975

Virus, Rous Sarcoma

Cell Membrane, 77-5706

Lipomatosis

Head and Neck Neoplasms

Review, 77-5439

LiverAcetamide, *N*-Fluoren-2-yl-

Ultrastructural Study, 77-5922

Aflatoxin B1

Metabolism, 77-5508

Aniline, *N,N*-Dimethyl-*p*-phenylazo-

Antigens, 77-5482

Antigens

Mouse, 77-5482

Antipyrine

Hydroxylases, 77-5569

Metabolism, 77-5569

Barbituric Acid, 5-(1-Cyclohexen-1-yl)-1,5-dimethyl-

Liver (cont'd)

Hydroxylases, 77-5569

Metabolism, 77-5569

Benz(a)anthracene, 5,6-Dihydro-5,6-epoxy-

Hydro-Lyases, 77-5543

Benzo(a)pyrene

Hydroxylases, 77-5569

Metabolism, 77-5566, 77-5569

Benzo(a)pyrene 4,5-Oxide

Hydro-Lyases, 77-5543

Benzo(a)pyrene 11,12-Oxide

Hydro-Lyases, 77-5543

Carbon Tetrachloride

Histological Study, Rat, 77-5547

Ultrastructural Study, Rat, 77-5547

Cholanthrene, 11,12-Dihydro-11,12-epoxy-3-methyl-

Hydro-Lyases, 77-5543

Cholanthrene, 3-Methyl-

Histological Study, Rat, 77-5547

Succinate Dehydrogenase, 77-5546

Ultrastructural Study, Rat, 77-5547

Coumarin

Hydroxylases, 77-5569

Metabolism, 77-5569

Coumarin, 7-Ethoxy-

Metabolism, 77-5569

Dibenz(a,h)anthracene

Histological Study, Rat, 77-5547

Ultrastructural Study, Rat, 77-5547

Dibenz(a,h)anthracene, 5,6-Dihydro-5,6-epoxy-

Hydro-Lyases, 77-5543

Dimethylamine, *N*-Nitroso-

Antigens, 77-5482

Rat, 77-5610

DNA Replication

Diet, 77-5991

Leukemia, Myelocytic

Neoplasm Metastasis, 77-5895

Naphthalene 1,2-Oxide

Hydro-Lyases, 77-5543

Ochratoxin A

Rat, 77-5515

Octene 1,2-Oxide

Hydro-Lyases, 77-5543

Ornithine Decarboxylase

Enzymatic Activity, 77-5991

Phenanthrene, 9,10-Dihydro-9,10-epoxy-

Hydro-Lyases, 77-5543

Phenanthrene, 9,10-Epoxy-9,10-dihydro-

Hydro-Lyases, 77-5543

Plutonium

Dog, 77-5662

Polyamines

DNA Replication, 77-5991

Prolactin

Binding, 77-5578

o-Toluidine, (4-*o*-tolylazo)-

Antigens, 77-5482

Liver Cirrhosis

Digestive System Neoplasms

Epidemiology, 77-5943

Dimethylamine, *N*-Nitroso-

Epidemiology, 77-5943

Ethyl Alcohol

Epidemiology, 77-5943

Liver Neoplasms

Smoking, 77-5943

Liver Cirrhosis (cont'd)

Mouth Neoplasms

Epidemiology, 77-5943

Pharyngeal Neoplasms

Epidemiology, 77-5943

Liver Neoplasms

Acetamide, *N*-Fluoren-2-yl-

Immunity, 77-5427

Review, 77-5415

Acetohydroxamic Acid, *N*-Fluoren-2-yl-

Review, 77-5415

Adenoma

Contraceptives, Oral, 77-5523

Cyprosterone Acetate, 77-5523

Epidemiology, 77-5525

Mestranol, 77-5525

19-Nor-17 α -pregn-4-en-20-yne-3 β ,17-diol, Diacetate
77-5523

Norethisterone, 77-5523

Norethynodrel, 77-5523

Rat, 77-5523

Angiosarcoma

Epidemiology, 77-5944, 77-5945

Ethylene, Chloro-, 77-5944

Ethylene, Chloro- Polymer, 77-5944

Aniline, *N,N*-Dimethyl-*p*-phenylazo-

Immunity, 77-5427

Antigens, Neoplasm

Review, 77-5427

Aroclor 1254

Metabolism, Trout, 77-5506

Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-

Selenium, 77-5480

Benzene, Hexachloro-

Hemangioendothelioma, 77-5483

Benzo(a)pyrene

Cells, Cultured, 77-5559

Metabolism, 77-5559

Transplacental Carcinogenesis, 77-5550

Biphenyl, 2,2',4,4',5,5'-Hexabromo-

Rat, 77-5486

Carcinoma

Epidemiology, 77-5525

Megestrol Acetate, 77-5523

Mestranol, 77-5525

Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)
77-5475

Norethynodrel, 77-5523

Rat, 77-5523

Cell Membrane

Glycoproteins, 77-5981

Contraceptives, Oral

Epidemiology, 77-5525

Diethylamine, *N*-Nitroso-

Cells, Cultured, 77-5919

Histological Study, 77-5919

Immunity, 77-5427

Dimethylamine, *N*-Nitroso-

Ascorbic Acid, 77-5599

Rat, 77-5599

Estradiol, 17-Ethynyl-

Epidemiology, 77-5525

Ethyl Alcohol

Epidemiology, 77-5943

Ethylene, Tetrachloro-

Carcinogenic Potential, 77-5408

Fetal Globulins

Liver Neoplasms (cont'd)

Review, 77-5427

Hemangioendothelioma

Arsenic, 77-5637

Hydrazine, 1,2-Dimethyl-

Hemangioendothelioma, 77-5500

Phosphonic Acid, (2,2,2-Trichloro-1-hydroxyethyl)-

Dimethyl Ester, 77-5500

Immunity

Review, 77-5427

Liver Cirrhosis

Epidemiology, 77-5943

Smoking, 77-5943

Mestranol

Estradiol, 17-Ethynyl-, 77-5525

Nitrous Acid, Sodium Salt

Rat, 77-5599

Preg-4-en-20-one, 17-(Acetyloxy)-6 α -methyl-

Dog, 77-5521

Pyrene

Transplacental Carcinogenesis, 77-5550

Smoking

Epidemiology, 77-5943

Liver Regeneration

Anise Oil

Rat, 77-5516

Blood Proteins

Isolation and Characterization, 77-5982

Cumin Oil

Rat, 77-5516

Estragon Oil

Rat, 77-5516

Fennel Oil

Rat, 77-5516

Mace Oil

Rat, 77-5516

Nutmeg Oil

Rat, 77-5516

Oils

Rat, 77-5516

Parsley Oil

Rat, 77-5516

Lucanthone

Cell Transformation, Neoplastic

Carcinogenic Potential, 77-5534

Nitrous Acid, Sodium Salt

Carcinogenic Potential, Rat, 77-5602

Virus, Rauscher Murine Leukemia

Cell Transformation, Neoplastic, 77-5534

Lung

Aryl Hydrocarbon Hydroxylases

Enzymatic Activity, 77-5590

Asbestos

Chemical Analysis, Fibers, 77-5647

Histological Study, 77-5953

Phagocytosis, 77-5647

Benzo(a)pyrene

Metabolism, 77-5566

Benzo(a)pyrene, 4,5-Dihydro-4,5-dihydroxy-

Metabolism, Hamster, 77-5563

Plutonium Oxide

Biochemical Study, Rat, 77-5661

Connective Tissue, 77-5661

Dose-Response Study, Mouse, 77-5660

Histological Study, Rat, 77-5661

Ultrastructural Study, Mouse, 77-5660

Lung (cont'd)

Smoking

- Acid Phosphatase, 77-5594
- Biochemical Study, Rat, 77-5594
- Collagen, 77-5594
- Elastin, 77-5594
- Glucuronidase, 77-5594
- Hexosamines, 77-5594
- Histological Study, 77-5595
- Urea, Methyl Nitroso-
Cells, Cultured, 77-5619

Lung Neoplasms

- Acetic Acid, Methylnitrosaminomethyl Ester
Dose-Response Study, Rat, 77-5611
- Acid Phosphatase
Enzymatic Activity, 77-5656
- Adenocarcinoma
Radiation, Ionizing, 77-5667
- Adenoma
Carbamic Acid, Ethyl Ester, 77-5498
- Methane, Tribromo-, 77-5493
- Water Pollutants, Chemical, 77-5493
- Alkaline Phosphatase
Enzymatic Activity, 77-5656
- Arsenic
Air Pollution, 77-5947
- Epidemiology, Sweden, 77-5947
- Occupational Hazard, 77-5947
- Asbestos
Case Report, 77-5954
- Water Pollution, 77-5957
- Asbestosis
Epidemiology, 77-5954
- Benzo(a)pyrene
Adenoma, 77-5550
- Mycobacterium bovis*, 77-5868
- Bronchi
Nitrosamines, 77-5603
- Carcinoma
Histological Study, 77-5667
- Carcinoma, Bronchogenic
Radiation, Ionizing, 77-5667
- Carcinoma, Epidermoid
Radiation, Ionizing, 77-5667
- Radon, 77-5419
- Dimethylamine, *N*-Nitroso-
Rat, 77-5599
- Dimethylamine, *N*-Nitroso-
Ascorbic Acid, 77-5599
- Dose-Response Study, Rat, 77-5611
- Dyes
Epidemiology, 77-5951
- Occupational Hazard, 77-5951
- Lactate Dehydrogenase
Enzymatic Activity, 77-5656
- Malate Dehydrogenase
Enzymatic Activity, 77-5656
- Mesothelioma
Asbestos, 77-5952, 77-5954
- Epidemiology, 77-5954
- Smoking, 77-5952
- Mycobacterium bovis*
Animal Model, Hamster, 77-5868
- Cell Wall, 77-5868
- Neoplasms, Radiation-Induced
Epidemiology, Review, 77-5419
- Nitrous Acid, Sodium Salt

Lung Neoplasms (cont'd)

- Rat, 77-5599
- Occupational Hazard
Epidemiology, 77-5948, 77-5951
- Epidemiology, Review, 77-5419
- Polonium
Hamster, 77-5657
- Histological Study, 77-5656, 77-5657
- Ultrastructural Study, 77-5657
- Pyrene
Adenoma, 77-5550
- Radiation, Ionizing
Histological Study, 77-5667
- Radon
Epidemiology, Review, 77-5419
- Smoking
Epidemiology, 77-5416, 77-5417
- Succinate Dehydrogenase
Enzymatic Activity, 77-5656

Lymphocyte Transformation

- Radiation, Ionizing
Chromosome Aberrations, 77-5650

Lymphocytes

- Arsenic
Cell Division, 77-5640
- Chromosome Aberrations, 77-5639, 77-5640
- DNA Replication, 77-5640
- Aryl Hydrocarbon Hydroxylases
Enzymatic Activity, 77-5588, 77-5590, 77-5591
- Smoking, 77-5591
- Benzo(a)pyrene
Cell-Cycle Kinetics, 77-5627
- Chromosome Aberrations, 77-5627
- Cells, Cultured
Chromosome Aberrations, 77-5628
- Cholanthrene, 3-Methyl-
Aryl Hydrocarbon Hydroxylases, 77-5588
- Chromosome Aberration
Ultraviolet Rays, 77-5672
- Chromosome Aberrations
Actinomycin D, 77-5628
- Psoralen, 8-Methoxy-, 77-5672
- Concanavalin A
Aryl Hydrocarbon Hydroxylases, 77-5588
- Diethylamine, *N*-Nitroso-
Cell-Cycle Kinetics, 77-5627
- Chromosome Aberrations, 77-5627
- Dimethylamine, *N*-Nitroso-
Cell-Cycle Kinetics, 77-5627
- Chromosome Aberrations, 77-5627
- Leukemia, Lymphocytic
Adenyl Cyclase, 77-5997
- Receptors, Hormone, 77-5997
- Methanesulfonic Acid, Ethyl Ester
Cell-Cycle Kinetics, 77-5627
- Chromosome Aberrations, 77-5627
- Methanesulfonic Acid, Methyl Ester
Cell-Cycle Kinetics, 77-5627
- Chromosome Aberrations, 77-5627
- Mitogens
Aryl Hydrocarbon Hydroxylases, 77-5588
- Mitomycin C
Cell-Cycle Kinetics, 77-5627
- Chromosome Aberrations, 77-5627
- Plant Agglutinins
Aryl Hydrocarbon Hydroxylases, 77-5588

Lymphocytes (cont'd)

- Radiation, Ionizing
 - Chromosome Aberrations, 77-5650
 - Plant Agglutinins, 77-5650
- Ultraviolet Rays
 - Immune Response, 77-5872
- Virus, C-Type RNA Tumor
 - Antigens, Viral, 77-5769

B-Lymphocytes

- Leukemia
 - Cell Membrane, 77-5663
- Leukemia, Lymphocytic
 - Review, 77-5446
- Multiple Myeloma
 - Review, 77-5446
- Radiation, Ionizing
 - Leukemia, 77-5663
- Sarcoma, Yoshida
 - Immune Response, 77-5876

T-Lymphocytes

- Histocompatibility Antigens
 - Immune Response, 77-5750
- Leukemia
 - Cell Membrane, 77-5663
- Lymphoma
 - Histocompatibility Antigens, 77-5750
 - Immune Response, 77-5750
- Radiation, Ionizing
 - Leukemia, 77-5663
- Rhabdomyosarcoma
 - Immune Response, 77-5863
- Sarcoma 180
 - Sarcoma 180, Crocker, 77-5862
- Sarcoma, Yoshida
 - Immune Response, 77-5876
- Virus, Radiation Leukemia
 - Immunity, Cellular, 77-5871
 - Macrophages, 77-5871

Lymphoma (General and Unspecified)

- Abdominal Neoplasms
 - Case Report, 77-5894
 - Histological Study, 77-5894
 - Sprue, 77-5894
- Ataxia Telangiectasia
 - Epidemiology, 77-5444
 - Immunologic Deficiency Syndromes, 77-5434
- Genetics
 - Immune Response, 77-5887
- Histocompatibility Antigens
 - Immune Response, 77-5750
- T-Lymphocytes
 - Histocompatibility Antigens, 77-5750
 - Immune Response, 77-5750
- Occupational Hazard
 - Epidemiology, 77-5948
- Radiation, Ionizing
 - Mouse, 77-5655
- Virus, Avian Leukosis
 - Epidemiology, Review, 77-5424
- Virus, Feline Leukemia
 - Antibodies, Viral, 77-5892
 - RNA, Viral, 77-5715
 - Viral Proteins, 77-5715
- Virus, Friend Murine Leukemia
 - Cells, Cultured, 77-5750
 - Immune Response, 77-5750

Lymphoma (General and Unspecified) (cont'd)

- Virus, Herpes Saimiri
 - Marmoset, 77-5808
- Virus, Marek's Disease Herpes
 - Epidemiology, Review, 77-5424
- Virus, Moloney Murine Sarcoma
 - Cells, Cultured, 77-5750
 - Immune Response, 77-5750
- Virus, RD-114
 - RNA, Viral, 77-5715
 - Viral Proteins, 77-5715
- Virus Replication
 - Marmoset, 77-5808

Lymphoma, Lymphocytic

see Lymphosarcoma

Lymphosarcoma

- DNA Polymerase
 - Fish, 77-5699
 - Isolation and Characterization, 77-5699
- Freund's Adjuvant
 - Immune Response, 77-5867
 - Immunologic Technics, 77-5867
- Histones
 - Mouse, 77-5857
- Virus, Bovine Leukemia
 - Antigens, Neoplasm, 77-5883

Lysosomes

- Sarcoma
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-5573
 - Cells, Cultured, 77-5573
 - Virus, Rous Sarcoma, 77-5573

Mace Oil

- Liver Regeneration
 - Rat, 77-5516

Macrophages

- Aryl Hydrocarbon Hydroxylases
 - Enzymatic Activity, 77-5590, 77-5591
 - Smoking, 77-5591
- Cell Differentiation
 - Cells, Cultured, 77-5963
- Sarcoma
 - Immune Response, 77-5874
- Smoking
 - Ultrastructural Study, 77-5593
- Ultraviolet Rays
 - Immune Response, 77-5872
- Virus, Friend Murine Leukemia
 - Immune Response, 77-5729
- Virus, Radiation Leukemia
 - Antigens, Viral, 77-5871
 - Immunity, Cellular, 77-5871
 - T-Lymphocytes, 77-5871

Malate Dehydrogenase

- Arsenic Acid, Sodium Salt
 - Mitochondria, Liver, 77-5642
- Lung Neoplasms
 - Enzymatic Activity, 77-5656

Mammary Neoplasms, Experimental

- Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-
 - Rat, 77-5462
- Adenocarcinoma
 - Carbamic Acid, Ethyl Ester, 77-5497
 - Virus, Murine Mammary Tumor, 77-5755

Mammary Neoplasms, Experimental (cont'd)

- Adenoma
 - Contraceptives, Oral, 77-5527
 - Dog, 77-5527
 - Ethynone, 77-5527
 - Histological Study, 77-5527
 - Mestranol, 77-5527
 - Preg-4-en-20-one, 17-Hydroxy-6 α -methyl-, 77-5527
 - Adenyl Cyclase
 - Mouse, 77-5992
 - Aldosterone
 - Cell Division, 77-5995
 - 5 α -Androstan-3-one, 17 β -Hydroxy-2 α -methyl-, Propionate
 - Neoplasm Regression, 77-5577
 - Benz(a)anthracene, 7,12-Dimethyl-5 α -Androstan-3-one, 17 β -Hydroxy-2 α -methyl-, Propionate, 77-5577
 - Azathioprine, 77-5579
 - Corynebacterium parvum*, 77-5579
 - Ergolines, 77-5577
 - Ergot Alkaloids, 77-5577
 - Estradiol, 77-5577
 - Hormones, 77-5996
 - Metabolism, Liver, 77-5574
 - Rat, 77-5578
- Benzo(a)pyrene
 - Transplacental Carcinogenesis, 77-5550
- Carbamic Acid, Methyl-, 1-Naphthyl Ester
 - Transplacental Carcinogenesis, Rat, 77-5600
- Carcinogen, Environmental
 - Mouse, 77-5648
- Cell Membrane
 - Glycoproteins, 77-5980
- Contraceptives, Oral
 - Dog, 77-5526
 - Histological Study, 77-5526
- Contraceptives, Oral, Hormonal
 - Adenocarcinoma, 77-5526
- Corticosterone
 - Cell Division, 77-5995
- Cortisol
 - Cell Division, 77-5995
- Ergolines
 - Neoplasm Regression, 77-5577
- Ergot Alkaloids
 - Neoplasm Regression, 77-5577
- Estradiol
 - Cell Division, 77-5995
 - Hormones, 77-5996
 - Neoplasm Regression, 77-5577
- Estradiol, 17-Ethynyl-
 - Dog, 77-5526
- Ethynone
 - Adenocarcinoma, 77-5521
 - Adenoma, 77-5521
 - Dog, 77-5521
 - Monkey, 77-5521
- Fatty Acids
 - Hormone Dependence, 77-5999
- Lipids
 - Hormone Dependence, 77-5999
- Melengestrol Acetate
 - Mouse, 77-5522
- Mestranol
 - Dog, 77-5521
 - Monkey, 77-5521

Mammary Neoplasms, Experimental (cont'd)

- Norgestrel, Chloroethynyl-
 - Adenocarcinoma, 77-5521
 - Adenoma, 77-5521
 - Dog, 77-5521
 - Monkey, 77-5521
 - Preg-4-en-20-one, 17-(Acetyloxy)-6 α -methyl-
 - Adenocarcinoma, 77-5521
 - Adenoma, 77-5521
 - Dog, 77-5521
 - Monkey, 77-5521
 - Pregnancy
 - Hormones, 77-5995
 - Progesterone
 - Cell Division, 77-5995
 - Mouse, 77-5524
 - Prolactin
 - Binding, 77-5578
 - Hormones, 77-5996
 - Progesterone, 77-5995
 - Pyrene
 - Transplacental Carcinogenesis, 77-5550
 - Testosterone
 - Cell Survival, 77-5996
 - Virus, Murine Mammary Tumor
 - Genetics, 77-5752
 - Strain Difference, 77-5755
- Manganese
 - DNA Replication
 - Carcinogenic Activity, 77-5634
 - Mutagenic Activity, 77-5634
- Medulloblastoma
 - Carcinoma, Basal Cell
 - Review, 77-5439
- Megestrol Acetate
 - Liver Neoplasms
 - Carcinoma, 77-5523
- Melanin
 - Melanoma
 - Tyrosine, 77-5986
 - Tyrosine
 - Cycloheximide, 77-5986
 - Urea, 1-Phenyl-2-thio-, 77-5986
- Melanoma
 - Asbestos
 - Epidemiology, 77-5955
 - Cells, Cultured
 - Peptide Hydrolases, 77-5985
 - Genetics
 - Review, 77-5447
 - Skin Neoplasms
 - Epidemiology, 77-5458, 77-5942
 - Ultraviolet Rays, 77-5942
 - Xeroderma Pigmentosum, 77-5434
 - Tyrosine
 - Melanin, 77-5986
 - Uridine, 5-Bromo-2'-deoxy-
 - Peptide Hydrolases, 77-5985
 - Virus, Baboon
 - Antibodies, Viral, 77-5810
 - Virus, C-Type RNA Tumor
 - Antibodies, Viral, 77-5810
 - Virus, Gibbon Ape Leukemia
 - Antibodies, Viral, 77-5810
 - Virus-Like Particles

- Melanoma (cont'd)**
 Ultrastructural Study, 77-5853
 Virus, Simian Sarcoma
 Antibodies, Viral, 77-5810
 Virus, Vesicular Stomatitis
 Alanine, 3-(3,4-Dihydroxyphenyl)-, 77-5853
 Ultrastructural Study, 77-5853
 Uridine, 2'-Deoxy-5-iodo-, 77-5853
 Virus-Like Particles, 77-5853
- Melengestrol Acetate**
 Mammary Neoplasms, Experimental
 Mouse, 77-5522
- Meningioma**
 Brain Neoplasms
 Guanyl Cyclase, 77-5993
 Chromosome Aberrations
 Review, 77-5435
- 6-Mercaptopurine**
 see Purine-6-thiol
- Mesothelioma**
 Asbestos
 Epidemiology, 77-5417
 Pleural Neoplasms, 77-5645
 Heart Neoplasms
 Ultrastructural Study, 77-5924
 Lung Neoplasms
 Asbestos, 77-5952, 77-5954
 Epidemiology, 77-5954
 Smoking, 77-5952
- Mestranol**
 Liver Neoplasms
 Adenoma, 77-5525
 Carcinoma, 77-5525
 Estradiol, 17-Ethynyl-, 77-5525
 Mammary Neoplasms, Experimental
 Adenoma, 77-5527
 Dog, 77-5521
 Monkey, 77-5521
- Metals**
 Toxicology
 Cells, Cultured, 77-5410
- Metaplasia**
 Cervix Neoplasms
 Cell Differentiation, 77-5453
 Mucus, 77-5453
- Methane**
 Colonic Neoplasms
 Carcinoma, 77-5476
- Methane, Azoxy-**
 Intestinal Neoplasms
 Candicidin, 77-5474
 Cholestyramine, 77-5474
- Methane, Tribromo-**
 Lung Neoplasms
 Adenoma, 77-5493
- Methanesulfonic Acid**
 Arsenic
 Excretion, Urine, 77-5641
 Arsenic Acid
 Excretion, Urine, 77-5641
 Arsenic Trioxide
 Excretion, Urine, 77-5641
- Methanesulfonic Acid, Ethyl Ester**
 Cells, Cultured
 Mutagenic Activity, 77-5632, 77-5680, 77-5681
 Chromosome Aberrations
 Cells, Cultured, 77-5629
 Lymphocytes
 Cell-Cycle Kinetics, 77-5627
 Chromosome Aberrations, 77-5627
- Methanesulfonic Acid, Methyl Ester**
 Chromosome Aberrations
 Cells, Cultured, 77-5629
Drosophila melanogaster, 77-5401
 DNA
 Alkylation, 77-5990
 DNA Repair
 Chromatin, 77-5626
 Endonucleases
 DNA Repair, 77-5990
 Glycoside Hydrolases
 DNA Repair, 77-5990
 Lymphocytes
 Cell-Cycle Kinetics, 77-5627
 Chromosome Aberrations, 77-5627
- Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)**
 Cells, Cultured
 Mutagenic Activity, 77-5536
 Liver Neoplasms
 Carcinoma, 77-5475
- Methanol, (Methyl-*ONN*-azoxy)-**
 Cells, Cultured
 Mutagenic Activity, 77-5537
- Methionine, *S*-Adenosyl-**
 Acetamide, *N*-Fluoren-2-yl-
 Liver, Rat, 77-5466
- O*-Methylguanine**
 see Purine, 2-Amino-6-methoxy-
- Methyltestosterone**
 see Androsta-1,4-dien-3-one, 17-Hydroxy-17-methyl-
- Microsomes, Liver**
 Acetamide, *N*-Fluoren-2-yl-
 Carcinogenic Metabolite, 77-5472
 Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 Carcinogenic Metabolite, 77-5472
 Benzo(a)pyrene
 Cytochrome P-450, 77-5555
 Cytochromes, 77-5555
 Hydroxylation, 77-5555
 NADPH Cytochrome C Reductase, 77-5555
 Bladder Neoplasms
 Carcinogenic Metabolite, 77-5472
 Glucuronidase, 77-5472
 Cholanthrene, 3-Methyl-
 Cytochrome P-448, 77-5554
 Hydroxylamine, *N*-4-Biphenyl-
 Carcinogenic Metabolite, 77-5472
 Hydroxylamine, *N*-1-Naphthyl-
 Carcinogenic Metabolite, 77-5472
 Hydroxylamine, *N*-2-Naphthyl-
 Carcinogenic Metabolite, 77-5472
 Hydroxylamine, *N*-(*p*-Phenylazo)phenyl-
 Carcinogenic Metabolite, 77-5472
- Mitochondria**
 Guanidine, 1-Methyl-3-nitro-1-nitroso-

- Mitochondria (cont'd)**
 DNA, 77-5623
 Quinoline-1-oxide, 4-Nitro-DNA, 77-5623
- Mitochondria, Liver**
 Arsenic Acid, Sodium Salt
 Cytochrome Oxidase, 77-5642
 Malate Dehydrogenase, 77-5642
 Mitochondrial Swelling, 77-5642
 Monoamine Oxidase, 77-5642
 Pyruvate Dehydrogenase Complex, 77-5643
 Ultrastructural Study, Rat, 77-5642
- Mitogens**
 Lymphocytes
 Aryl Hydrocarbon Hydroxylases, 77-5588
- Mitomycin C**
 Chromosome Aberrations
 Cells, Cultured, 77-5629
 Lymphocytes
 Cell-Cycle Kinetics, 77-5627
 Chromosome Aberrations, 77-5627
- Mixed Function Oxidases**
see also Oxidoreductases
 Dimethylamine, *N*-Nitroso-Metabolism, 77-5609
- Monoamine Oxidase**
 Arsenic Acid, Sodium Salt
 Mitochondria, Liver, 77-5642
 Dimethylamine, *N*-Nitroso-Metabolism, 77-5609
- Monocrotaline**
 Retronecine, 3,8-Didehydro-Carcinogenic Metabolite, 77-5505
- Morpholine, *N*-Nitroso-**
 Nitrous Acid
Saccharomycopsis lipolytica, 77-5604
- Mouth Neoplasms**
 Asbestos
 Epidemiology, 77-5955
 Benz(a)anthracene, 7,12-Dimethyl-Cell-Cycle Kinetics, 77-5572
 Carcinogen, Environmental
 Epidemiology, 77-5459
 Carcinoma
 Benz(a)anthracene, 7,12-Dimethyl-, 77-5571
 Hamster, 77-5571
 Histological Study, 77-5571
 Ethyl Alcohol
 Epidemiology, 77-5943
 Liver Cirrhosis
 Epidemiology, 77-5943
 Smoking
 Epidemiology, 77-5416, 77-5459, 77-5943
 Tobacco
 Alcohol Drinking, 77-5416
 Epidemiology, 77-5459
- Multiple Myeloma**
 Antineoplastic Agents
 Cell Survival, 77-5962
 Ethnic Groups
 Epidemiology, 77-5458
 Genetics
 Antibody Formation, 77-5875
- Multiple Myeloma (cont'd)**
 Blood Proteins, 77-5875
 Immunoglobulins, 77-5875
- IgG**
 Growth, 77-5962
- B-Lymphocytes**
 Review, 77-5446
 Occupational Hazard
 Epidemiology, 77-5948
- Mutagens**
 DNA Repair
 Quantitation Method, Review, 77-5411
- Mycobacterium bovis***
 Lung Neoplasms
 Animal Model, Hamster, 77-5868
 Benzo(a)pyrene, 77-5868
 Cell Wall, 77-5868
- Mycotoxins**
 Aflatoxin B1
 Histological Study, Duck, Goat, 77-5512
 Breast Neoplasms
 Food Contamination, 77-5414
 Diet
 Review, 77-5460
 Versiconal Hemiacetal Acetate
 Biosynthesis, 77-5509
- Myxosarcoma**
 Nose Neoplasms
 Epidemiology, 77-5950
- NADPH**
 Benzo(a)pyrene
 Aryl Hydrocarbon Hydroxylases, 77-5544
 Benzo(b)triphenylene
 Aryl Hydrocarbon Hydroxylases, 77-5544
 Cholanthrene, 3-Methyl-Aryl Hydrocarbon Hydroxylases, 77-5544
 Dibenz(a,h)anthracene
 Aryl Hydrocarbon Hydroxylases, 77-5544
 DNA
 Binding, 77-5544
- NADPH Cytochrome C Reductase**
 Benzo(a)pyrene
 Microsomes, Liver, 77-5555
- Nafenopin**
 Amino Acids
 Liver, Rat, 77-5531
 Carboxy-Lyases
 Liver, Rat, 77-5531
 DNA Replication
 Liver, Rat, 77-5531
- Naphthalene**
Cunninghamella elegans
 Carcinogenic Metabolite, 77-5541
 Naphthalene, 1,2-Dihydro-1,2-dihydroxy-Carcinogenic Metabolite, 77-5541
 1-Naphthol
 Carcinogenic Metabolite, 77-5541
 2-Naphthol
 Carcinogenic Metabolite, 77-5541
 1,2-Naphthoquinone
 Carcinogenic Metabolite, 77-5541
 1,4-Naphthoquinone
 Carcinogenic Metabolite, 77-5541

Naphthalene (cont'd)

Oxidation

Carcinogenic Metabolite, 77-5541

1-Tetralone, 4-Hydroxy-

Carcinogenic Metabolite, 77-5541

Naphthalene, 1,2-Dihydro-1,2-dihydroxy-

Naphthalene

Carcinogenic Metabolite, 77-5541

Oxidation

Carcinogenic Metabolite, 77-5541

Naphthalene 1,2-Oxide

Liver

Hydro-Lyases, 77-5543

1-Naphthol

Naphthalene

Carcinogenic Metabolite, 77-5541

Oxidation

Carcinogenic Metabolite, 77-5541

2-Naphthol

Naphthalene

Carcinogenic Metabolite, 77-5541

Oxidation

Carcinogenic Metabolite, 77-5541

1,2-Naphthoquinone

Naphthalene

Carcinogenic Metabolite, 77-5541

Oxidation

Carcinogenic Metabolite, 77-5541

1,4-Naphthoquinone

Naphthalene

Carcinogenic Metabolite, 77-5541

Oxidation

Carcinogenic Metabolite, 77-5541

1,4-Naphthoquinone, 2-Methyl-

Cells, Cultured

Metabolism, 77-5625

Nasopharyngeal Neoplasms

Antibodies, Viral

Epidemiology, 77-5824, 77-5934

Carcinoma

Antibodies, Viral, 77-5822

Neoplasm Transplantation, 77-5859

Virus, Epstein-Barr, 77-5459, 77-5822, 77-5823
77-5824, 77-5934

Genetics

Epidemiology, 77-5935

Histocompatibility Antigens

Epidemiology, 77-5935

Histological Study

Mouse, 77-5859

Neoplasm Transplantation

Mouse, 77-5859

Virus, Epstein-Barr

Antibodies, Viral, 77-5823, 77-5824

Epidemiology, 77-5457

Immune Response, 77-5935

Neoplasm Metastasis

Breast Neoplasms

Carcinoma, 77-5930

Cervix Neoplasms

Ultrastructural Study, 77-5911

Hepatoma

Heptachlor, 77-5490

Neoplasm Metastasis (cont'd)

Heptachlor Epoxide, 77-5490

Leukemia, Myelocytic

Liver, 77-5895

Transplantation, Homologous, 77-5895

Ultrastructural Study, 77-5895

Pancreatic Neoplasms

Epidemiology, Review, 77-5449

Paranasal Sinus Neoplasms

Cesium Chloride, 77-5666

Teratoid Tumor

Ultrastructural Study, 77-5914

Neoplasm Regression, Spontaneous

Leukemia, Lymphocytic

Antibody Formation, 77-5731

Virus, Friend Murine Leukemia, 77-5731

Virus, Helper, 77-5731

Virus, Friend Murine Leukemia

Virus, Helper, 77-5731

Neoplasm Transplantation

Carbamic Acid, Ethyl Ester

Mouse, 77-5497

Corticotropin

Mouse, 77-5528

Cortisol

Mouse, 77-5528

Nasopharyngeal Neoplasms

Carcinoma, 77-5859

Mouse, 77-5859

Stress

Mouse, 77-5528

Neoplasms (General and Unspecified)

Aquatic Animals

Epidemiology, Review, 77-5404, 77-5405

Ataxia Telangiectasia

Statistical Analysis, 77-5440

Breast Neoplasms

Genetics, 77-5442

Carbon Tetrachloride

Fish, 77-5958

Cell Line

Carcinogenic Potential, 77-5906

Chloroform

Fish, 77-5958

Chromosome Aberrations

Models, Theoretical, 77-5430

Epidemiology

Review, 77-5457

Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-

Fish, 77-5958

Ethylene, Chloro-

Occupational Hazard, 77-5417

Ethylene, Chloro- Polymer

Occupational Hazard, 77-5417

Fish

Epidemiology, Review, 77-5404

Histological Study, 77-5958

Genetics

Epidemiology, 77-5441, 77-5442, 77-5456, 77-5904

Immune Response, 77-5441

Review, 77-5436

Hereditary Diseases

Inbreeding, Review, 77-5437

Karyotyping

Cell Line, 77-5906

Occupational Hazard

Neoplasms (General and Unspecified) (cont'd)

- Epidemiology, 77-5948
- Pesticides
 - Fish, 77-5958
- Sarcoma
 - Genetics, 77-5442
- Water Pollution
 - Epidemiology, 77-5956
 - Fish, 77-5958
- Neoplasms, Experimental**
 - Beryllium
 - Trace Elements, Review, 77-5412
 - Cadmium
 - Trace Elements, Review, 77-5412
 - Cell Transformation, Neoplastic
 - Isolation and Characterization, 77-5969
 - Cholanthrene, 3-Methyl-
 - Stress, 77-5586
 - Temperature, 77-5586
 - Chromium
 - Trace Elements, Review, 77-5412
 - Cobalt
 - Trace Elements, Review, 77-5412
 - Iron
 - Trace Elements, Review, 77-5412
 - Lead
 - Trace Elements, Review, 77-5412
 - Nickel Sulfide
 - Trace Elements, Review, 77-5412
 - Virus, Adeno 12
 - Histological Study, 77-5803
 - Virus, Moloney Murine Sarcoma
 - Adenosine Cyclic 3',5' Monophosphate, 77-5746
 - Guanosine Cyclic 3',5' Monophosphate, 77-5746
 - Prostaglandins E, 77-5746
 - Prostaglandins F, 77-5746
 - Virus, Para-Adeno 12
 - Histological Study, 77-5803
 - Virus, Rous Sarcoma
 - Immune Response, Chicken, 77-5865
 - Virus, SV40
 - Histological Study, 77-5803

Neoplasms, Multiple Primary

- Breast Neoplasms
 - Genetics, 77-5442
- Genetics
 - Case Report, 77-5903
 - Epidemiology, 77-5442
- Hamartoma
 - Genetics, 77-5903
- Sarcoma
 - Genetics, 77-5442
- Urogenital Neoplasms
 - Genetics, 77-5936

Neoplasms, Radiation-Induced

- Child
 - Irradiation, Fetal, 77-5683
- Fetus
 - Leukemia, Lymphocytic, 77-5683
- Lung Neoplasms
 - Epidemiology, Review, 77-5419
- Sarcoma, Osteogenic
 - C-Type Particles, 77-5764
 - Virus, C-Type RNA Tumor, 77-5764
- Virus, C-Type RNA Tumor
 - Virus Replication, 77-5764

Neoplasms, Vascular Tissue

- Spleen
 - Reverse Transcriptase, 77-5848
 - RNA, Viral, 77-5848
 - Virus-Like Particles, 77-5848
- Virus-Like Particles
 - Ultrastructural Study, Spleen, 77-5848

Nephroblastoma

- Breast Neoplasms
 - Radiotherapy, 77-5689
- Case Report
 - Histological Study, 77-5913
 - Ultrastructural Study, 77-5913
- Endometriosis
 - Case Report, 77-5913
- Ethnic Groups
 - Epidemiology, 77-5458
- Hamartoma
 - Epidemiology, 77-5444
- Histological Study
 - Review, 77-5445
- Radiation, Ionizing
 - Irradiation, Fetal, 77-5683

Nervous System Neoplasms

- Urea, Ethyl Nitroso-
 - Rat, 77-5615

Neurilemmoma

- Brain Neoplasms
 - Guanyl Cyclase, 77-5993
- Urea, Ethyl Nitroso-
 - Histological Study, 77-5615

Neuroblastoma

- Chromosome Aberrations
 - Ultrastructural Study, 77-5902
- Ethnic Groups
 - Epidemiology, 77-5458
- Genetics
 - Review, 77-5447
- Histological Study
 - Review, 77-5445
- Radiation, Ionizing
 - Irradiation, Fetal, 77-5683

Nickel

- Adenocarcinoma
 - Rat, 77-5635
- Carcinogenic Potential
 - Case Report, 77-5635
 - Epidemiology, 77-5635
- Carcinoma
 - Rat, 77-5635
- DNA Replication
 - Carcinogenic Activity, 77-5634
 - Mutagenic Activity, 77-5634
- Occupational Hazard
 - Trace Elements, Review, 77-5412
- Rhabdomyosarcoma
 - Rat, 77-5635
- Sarcoma
 - Rat, 77-5635

Nickel Carbonyl

- Carcinogenic Potential
 - Epidemiology, 77-5635

Nickel Sulfide

- Neoplasms, Experimental

- Nickel Sulfide (cont'd)**
Trace Elements, Review, 77-5412
- Nitric Acid**
Hydatidiform Mole
Water Pollutants, 77-5598
- Nitrite**
see Nitrous Acid
- Nitrosamines**
Lung Neoplasms
Bronchi, 77-5603
Stomach Neoplasms
Diet, 77-5460
- Nitroso Compounds**
Esophageal Neoplasms
Epidemiology, 77-5459
- Nitrous Acid**
1-Butanamine, *N*-Butyl-*N*-nitroso-
Saccharomycopsis lipolytica, 77-5604
Diethylamine, *N*-Nitroso-
Saccharomycopsis lipolytica, 77-5604
Dimethylamine, *N*-Nitroso-
Saccharomycopsis lipolytica, 77-5604
Dipentylamine, *N*-Nitroso-
Saccharomycopsis lipolytica, 77-5604
1-Hexanamine, *N*-Hexyl-*N*-nitroso-
Saccharomycopsis lipolytica, 77-5604
Morpholine, *N*-Nitroso-
Saccharomycopsis lipolytica, 77-5604
Piperidine, 1-Nitroso-
Saccharomycopsis lipolytica, 77-5604
Salmonella typhimurium
Mutagenic Activity, 77-5601
Stomach Neoplasms
Food, 77-5601
- Nitrous Acid, Sodium Salt**
Arginine
Carcinogenic Potential, Rat, 77-5602
Carbamic Acid, Methyl-, 1-Naphthyl Ester
Transplacental Carcinogenesis, Rat, 77-5600
Chlordiazepoxide
Carcinogenic Potential, Rat, 77-5602
Dimethylamine
Nitrosamine Formation, 77-5610
Dodecylamine, *N,N*-Dimethyl-
Carcinogenic Potential, Rat, 77-5602
Guanidine, Methyl-
Carcinogenic Potential, Rat, 77-5602
Hexamethylenetetramine
Carcinogenic Potential, Rat, 77-5602
Kidney Neoplasms
Rat, 77-5599
Liver Neoplasms
Rat, 77-5599
Lucanthone
Carcinogenic Potential, Rat, 77-5602
Lung Neoplasms
Rat, 77-5599
Phenothiazine, 2-Chloro-10-(3-(dimethylamino)propyl)-
Carcinogenic Potential, Rat, 77-5602
Piperazine, 1-(Diphenylmethyl)-4-methyl-
Carcinogenic Potential, Rat, 77-5602
Piperdine
Carcinogenic Potential, Rat, 77-5602
Piperonyl Butoxide
- Nitrous Acid, Sodium Salt (cont'd)**
Carcinogenic Potential, Rat, 77-5602
Pyridine, 2-(2-((Dimethylamino)ethyl)-2-thenylamino)-
Carcinogenic Potential, Rat, 77-5602
Trimethylamine, *N*-Oxide
Carcinogenic Potential, Rat, 77-5602
Urea, *N,N*-Dimethyl-*N*-phenyl-
Carcinogenic Potential, Rat, 77-5602
- 19-Nor-17 α -pregn-4-en-20-yne-3 β ,17-diol, Diacetate**
Liver Neoplasms
Adenoma, 77-5523
- Norethisterone**
Liver Neoplasms
Adenoma, 77-5523
- Norethynodrel**
Liver Neoplasms
Adenoma, 77-5523
Carcinoma, 77-5523
- Norgestrel, Chloroethynyl-**
Mammary Neoplasms, Experimental
Adenocarcinoma, 77-5521
Adenoma, 77-5521
Dog, 77-5521
Monkey, 77-5521
- Norharman**
Salmonella typhimurium
Mutagenic Activity, 77-5479
- Norsolorinic Acid**
Aflatoxin B1
Mutagenic Activity, Biosynthetic Intermediates
77-5510
- Nose Neoplasms**
Adenocarcinoma
Epidemiology, 77-5950
Carcinoma
Epidemiology, 77-5950
Carcinoma, Epidermoid
Epidemiology, 77-5950
Myxosarcoma
Epidemiology, 77-5950
- Nucleic Acids**
Photochemistry
Ultraviolet Rays, 77-5420
- Nucleoproteins**
Uridine, 5-Bromo-2'-deoxy-
DNA, Binding, 77-5984
Embryo, Rat, 77-5984
- Nucleotides**
Exonucleases
Enzymatic Activity, 77-5535
- Nutmeg Oil**
Liver Regeneration
Rat, 77-5516
- Occupational Hazard**
Arsenic
Chromosome Aberrations, 77-5639
Trace Elements, Review, 77-5412
Arsenic Trioxide
Epidemiology, 77-5636
Asbestos
Phagocytosis, 77-5647

- Occupational Hazard (cont'd)**
- Bladder Neoplasms
 - Epidemiology, 77-5417
 - Breast Neoplasms
 - Epidemiology, 77-5946, 77-5951
 - Carcinogen, Chemical
 - Legislation, 77-5949
 - Carcinogen, Environmental
 - Epidemiology, 77-5417
 - Digestive System Neoplasms
 - Arsenic Trioxide, 77-5636
 - Epidemiology, 77-5946
 - Ethylene, Chloro- Polymer
 - Epidemiology, 77-5946
 - Gynecologic Neoplasms
 - Epidemiology, 77-5951
 - Hodgkin's Disease
 - Epidemiology, 77-5948
 - Intestinal Neoplasms
 - Epidemiology, 77-5946
 - Leukemia
 - Epidemiology, 77-5948
 - Lung Neoplasms
 - Arsenic, 77-5947
 - Dyes, 77-5951
 - Epidemiology, 77-5948, 77-5951
 - Epidemiology, Review, 77-5419
 - Lymphoma
 - Epidemiology, 77-5948
 - Multiple Myeloma
 - Epidemiology, 77-5948
 - Neoplasms
 - Epidemiology, 77-5948
 - Ethylene, Chloro-, 77-5417
 - Ethylene, Chloro- Polymer, 77-5417
 - Respiratory Tract Neoplasms
 - Arsenic Trioxide, 77-5636
 - Styrene
 - Metabolism, Review, 77-5495
 - Urogenital Neoplasms
 - Epidemiology, 77-5946
- Ochratoxin A**
- Kidney
 - Rat, 77-5515
 - Liver
 - Rat, 77-5515
- Octene 1,2-Oxide**
- Liver
 - Hydro-Lyases, 77-5543
- Oils**
- Anisole, *p*-Allyl-
 - Liver Regeneration, Rat, 77-5516
 - Anisole, *p*-Propenyl-
 - Liver Regeneration, Rat, 77-5516
 - Benzaldehyde, *p*-Isopropyl-
 - Liver Regeneration, Rat, 77-5516
 - Benzene, 4-Allyl-1,2-(methylenedioxy)-
 - Liver Regeneration, Rat, 77-5516
 - Benzene, 1,2-(Methylenedioxy)-4-propenyl-
 - Liver Regeneration, Rat, 77-5516
- Oligodendroglioma**
- Brain Neoplasms
 - Guanyl Cyclase, 77-5993
- Oligonucleotides**
- Virus, Murine Leukemia
- Oligonucleotides (cont'd)**
- Mice, AKR, 77-5768
 - Ribonuclease Resistance, 77-5768
 - RNA, Viral, 77-5768
- Oligopeptides**
- Bladder Neoplasms
 - 1-Butanol, 4-(Butylnitrosamino)-, 77-5606
 - Cell Transformation, Neoplastic, 77-5606
- Oncogenic Viruses**
- DNA
 - Carcinogenesis Model, Review, 77-5432
- Organ Culture**
- Bladder
 - Hyperplasia, 77-5977
- Ornithine Decarboxylase**
- Diet
 - Enzymatic Activity, 77-5991
- Ornithine Decarboxylase**
- Liver
 - Enzymatic Activity, 77-5991
- Osteosarcoma**
- see Sarcoma, Osteogenic
- Ovarian Neoplasms**
- Breast Neoplasms
 - Epidemiology, US, 77-5932
 - Carcinoid Tumor
 - Case Report, 77-5917
 - Histological Study, 77-5917
 - Ultrastructural Study, 77-5917
 - Hydrazine, 1,2-Dimethyl-
 - Hemangioma, 77-5500
 - Phosphonic Acid, (2,2,2-Trichloro-1-hydroxyethyl)-
 - Dimethyl Ester, 77-5500
 - Leukemia
 - Statistical Analysis, 77-5440
- Oxidoreductases**
- Acetamide, *N*-Fluoren-2-yl-
 - Liver, Rat, 77-5466
 - Benzo(a)pyrene
 - Uridine Diphosphate Sugars, 77-5564
- Pancreatic Neoplasms**
- Acetamide, *N*-Fluoren-2-yl-
 - Epidemiology, Review, 77-5449
 - Asbestos
 - Water Pollution, 77-5957
 - Carbamic Acid, Nitro-, Ethyl Ester
 - Epidemiology, Review, 77-5449
 - Cholanthrene, 3-Methyl-
 - Epidemiology, Review, 77-5449
 - Dipropylamine, 2,2'-Dioxo-*N*-nitroso-
 - Carcinogenic Activity, Hamster, 77-5607
 - Giant Cell Tumors
 - Histological Study, 77-5923
 - Ultrastructural Study, 77-5923
 - Jaundice, Obstructive
 - Epidemiology, Review, 77-5449
 - Neoplasm Metastasis
 - Epidemiology, Review, 77-5449
 - Smoking
 - Epidemiology, Review, 77-5449
- Papilloma**
- Eels

Epithelioma (cont'd)

- Epidemiology, 77-5959
- Histological Study, 77-5959

Skin Neoplasms

- Fluoclorolone Acetonide, 77-5540
- Fluocinolone Acetonide, 77-5540
- 12-*O*-Tetradecanoylphorbol-13-acetate, 77-5540

Tongue Neoplasms

- Quinoline, 4-Nitro-, 1-Oxide, 77-5624

Virus, RNA Tumor

- Epidemiology, Eels, Review, 77-5426

Water Pollution

- Epidemiology, Eels, Review, 77-5426

Traganglioma, Nonchromaffin**Genetics**

- Review, 77-5439, 77-5447

Tranasal Sinus Neoplasms**Carcinoma, Epidermoid**

- Cesium Chloride, 77-5666

Cesium Chloride

- Neoplasm Metastasis, 77-5666

Trity**Breast Neoplasms**

- Epidemiology, US, 77-5932

Cervix Neoplasms

- Epidemiology, Nigeria, 77-5927

Trisley Oil**Liver Regeneration**

- Rat, 77-5516

Tulin**Food Contamination**

- Isolation and Characterization, 77-5514

Tetradecan-2-one**HeLa Cells**

- Cell Adhesion, 77-5974

Tide Hydrolases**Melanoma**

- Cells, Cultured, 77-5985

Uridine, 5-Bromo-2'-deoxy-

- Melanoma, 77-5985

Tides**Virus, Hamster Sarcoma**

- Cell Transformation, Neoplastic, 77-5774

Tritoneal Neoplasms**Asbestos**

- Epidemiology, 77-5955

Oxidases**Cytochrome P-450**

- Enzyme Activation, 77-5491
- Molecular Orbital Calculations, 77-5491

Oxyacetic Acid, Trifluoro-**Cytochrome P-450**

- Enzyme Activation, 77-5491
- Molecular Orbital Calculations, 77-5491

Oxyacetyl Nitrate**Skin Neoplasms**

- Oxidants, Chemical, Review, 77-5418

Ultraviolet Rays

- Co-carcinogenic Effect, Review, 77-5418

Pesticides**Fibrosarcoma****Pesticides (cont'd)**

- Fish, 77-5958

Neoplasms

- Fish, 77-5958

Phagocytosis**Asbestos**

- Lung, 77-5647

- Occupational Hazard, 77-5647

Pharyngeal Neoplasms

- Carcinogen, Environmental

- Epidemiology, 77-5459

Liver Cirrhosis

- Epidemiology, 77-5943

Phenanthrene**Coliphages**

- DNA, 77-5545

- RNA, 77-5545

Phenanthrene, 9,19-Dihydro-9,10-epoxy-**Liver**

- Hydro-Lyases, 77-5543

Phenol, (1,1-Dimethylethyl)-4-methoxy-

- Dimethylamine, *N*-Nitroso-

- Rat, 77-5610

Phenothiazine, 2-Chloro-10-(3-(dimethylamino)propyl)-

- Nitrous Acid, Sodium Salt

- Carcinogenic Potential, Rat, 77-5602

***o*-Phenylenediamine, 4-Nitro-**

- Chromosome Aberrations

- Review, 77-5435

Pheochromocytoma**Asbestos**

- Hamster, 77-5644

Genetics

- Review, 77-5447

- Phosphoric Acid, Titanium Salt

- Hamster, 77-5644

Phorbol 12,3-Didecanoate

- Cholanthrene, 3-Methyl-

- DNA Replication, 77-5539

DNA Replication

- Cells, Cultured, 77-5539

Phorbol Myristate Acetate

- see* 12-*O*-Tetradecanoylphorbol-13-acetate

Phosphine Sulfide, Tris(1-aziridinyl)-

- Chromosome Aberrations

- Cells, Cultured, 77-5629

Phosphodiesterases**Hepatoma**

- Butyric Acid, 2-Amino-4-(ethylthio)-, 77-5499

Phosphoinositides**Benzo(a)pyrene**

- Cell Transformation, Neoplastic, 77-5968

- Growth Substances, 77-5968

Virus, SV40

- Cell Transformation, Neoplastic, 77-5968

- Growth Substances, 77-5968

Phosphonic Acid, (2,2,2-Trichloro-1-hydroxyethyl)- Dimethyl Ester

- Intestinal Neoplasms

- Hydrazine, 1,2-Dimethyl-, 77-5500

Liver Neoplasms

- Hydrazine, 1,2-Dimethyl-, 77-5500

Ovarian Neoplasms

- Hydrazine, 1,2-Dimethyl-, 77-5500

- Phosphonic Acid, (2,2,2-Trichloro-1-hydroxyethyl)- Dimethyl Ester (cont'd)**
 Uterine Neoplasms
 Hydrazine, 1,2-Dimethyl-, 77-5500
- Phosphoproteins**
 Virus, Murine Leukemia
 Isolation and Characterization, 77-5725
 Virus, Rauscher Murine Leukemia
 Isolation and Characterization, 77-5725
- Phosphoric Acid, 2,2-Dichlorovinyl-, Dimethyl Ester**
 Versiconal Hemiacetal Acetate
 Biosynthesis, 77-5509
- Phosphoric Acid, Titanium Salt**
 Abdominal Neoplasms
 Hamster, 77-5644
 Hemangioendothelioma
 Hamster, 77-5644
 Histological Study
 Rat, 77-5644
 Pheochromocytoma
 Hamster, 77-5644
 Sarcoma, Reticulum Cell
 Rat, 77-5644
- Piperazine, 1,4-Dinitroso-**
 Bronchi
 DNA, Binding, 77-5603
 Metabolism, 77-5603
- Piperazine, 1-(Diphenylmethyl)-4-methyl-**
 Nitrous Acid, Sodium Salt
 Carcinogenic Potential, Rat, 77-5602
- Piperidine**
 Nitrous Acid, Sodium Salt
 Carcinogenic Potential, Rat, 77-5602
- Piperidine, 1-Nitroso-**
 Nitrous Acid
Saccharomycopsis lipolytica, 77-5604
- Piperonyl Butoxide**
 Nitrous Acid, Sodium Salt
 Carcinogenic Potential, Rat, 77-5602
- Pituitary Neoplasms**
 Carbamic Acid, Methyl-, 1-Naphthyl Ester
 Transplacental Carcinogenesis, Rat, 77-5600
- Plant Agglutinins**
 Cell Membrane
 Binding, 77-5979
 Cells, Cultured, 77-5979
 Lymphocytes
 Aryl Hydrocarbon Hydroxylases, 77-5588
 Radiation, Ionizing
 Lymphocytes, 77-5650
 Virus, Epstein-Barr
 Antigens, Viral, 77-5821
- Plant Tumors**
Agrobacterium tumefaciens
 DNA, Bacterial, 77-6000
 Extrachromosomal Inheritance, 77-6000
 Plasmids, 77-6000
- Plasmacytoma**
 C.I. Direct Violet 100
 Rat, 77-5478
 RNA, Messenger
- Plasmacytoma (cont'd)**
 DNA-RNA Hybridization, 77-5989
 Virus, Abelson Murine Leukemia
 Virus-Like Particles, A-Type, 77-5770
- Plasminogen**
 Virus, SV40
 Cell-Cycle Kinetics, 77-5784
 Cells, Cultured, 77-5784
- Platinum, Diaminedichloro-, cis-**
 Cells, Cultured
 Mutagenic Activity, 77-5681
- Pleural Neoplasms**
 Asbestos
 Diagnosis and Prognosis, 77-5645
 Epidemiology, 77-5645, 77-5955
 Mesothelioma, 77-5645
- Plutonium**
 Bone and Bones
 Dog, 77-5662
 Histological Study, Hamster, Rabbit, 77-5659
 Liver
 Dog, 77-5662
 Water Pollution
 Food Chain, 77-5658
- Plutonium Oxide**
 Lung
 Biochemical Study, Rat, 77-5661
 Connective Tissue, 77-5661
 Dose-Response Study, Mouse, 77-5660
 Histological Study, Rat, 77-5661
 Ultrastructural Study, Mouse, 77-5660
- Polonium**
 Lung Neoplasms
 Hamster, 77-5657
 Histological Study, 77-5656, 77-5657
 Ultrastructural Study, 77-5657
- Polonium Radioisotopes**
 Water Pollution
 Food Chain, 77-5658
- Polyamines**
 DNA Replication
 Diet, 77-5991
 Liver, 77-5991
- Polychlorobiphenyl Compounds**
 Adipose Tissue
 Metabolism, Review, 77-5495
 Metabolism
 Rat, 77-5484
- Polycyclic Hydrocarbons**
 Carbon Tetrachloride
 Free Radicals, 77-5547
 Coliphages
 DNA, 77-5545
 RNA, 77-5545
 Colonic Neoplasms
 Diet, 77-5460
 Esophageal Neoplasms
 Epidemiology, 77-5459
 Fish
 Tissue Concentrations, 77-5549
 Smoking
 Condensate, Cigarette, 77-5596

Polycyclic Hydrocarbons (cont'd)

- Soot
 - Carcinogenic Activity, Mouse, 77-5552
- Tobacco
 - Isolation and Characterization, Pyrolyzate, 77-5596

Polycythemia Vera

- Hematopoietic Stem Cells
- Review, 77-5446

Phosphatidylcholine

- see Lecithins

Precancerous Conditions

- Breast Neoplasms
 - Diagnosis and Prognosis, 77-5929
 - Epidemiology, 77-5929
- Cervix Neoplasms
 - Ultrastructural Study, 77-5911
- Gastrointestinal Neoplasms
 - Glycoproteins, Review, 77-5451
- Hepatoma
 - Animal Model, Rat, 77-5920
 - Urea, Ethyl Nitroso-, 77-5614
- Tongue Neoplasms
 - Quinoline, 4-Nitro-, 1-Oxide, 77-5624

Progesterone

- Cell Transformation, Neoplastic
 - Growth, 77-5782
- Cells, Cultured
 - Growth, 77-5782

Prog-4-en-20-one, 17-(Acetyloxy)-6 α -methyl-

- Liver Neoplasms
 - Dog, 77-5521
- Mammary Neoplasms, Experimental
 - Adenocarcinoma, 77-5521
 - Adenoma, 77-5521
 - Dog, 77-5521
 - Monkey, 77-5521

Prog-4-en-20-one, 17-Hydroxy-6 α -methyl-

- Mammary Neoplasms, Experimental
 - Adenoma, 77-5527

Pregnancy

- Mammary Neoplasms, Experimental
 - Hormones, 77-5995
- Virus, Gross Murine Leukemia
 - Antibodies, Viral, 77-5739

Pneumonia

- Radiation, Ionizing
 - DNA Repair, 77-5433

Progesterone

- Mammary Neoplasms, Experimental
 - Cell Division, 77-5995
 - Mouse, 77-5524
 - Prolactin, 77-5995

Prolactin

- Breast Neoplasms
 - Cell Survival, 77-5996
- Liver
 - Binding, 77-5578
- Mammary Neoplasms, Experimental
 - Binding, 77-5578
 - Hormones, 77-5996
 - Progesterone, 77-5995
- Virus, Murine Mammary Tumor

Prolactin (cont'd)

- Virus Replication, 77-5754
- Virus Replication
 - Cells, Cultured, 77-5754
- Propane, 1-Chloro-2,3-epoxy-*Salmonella typhimurium*
 - Mutagenic Activity, 77-5488
- 1,3-Propanediamine
 - DNA Replication
 - Diet, 77-5991
- 2-Propen-1-amine, *N*-Nitroso-*N*-2-propenyl-
 - Respiratory Tract Neoplasms
 - Dose-Response Study, Hamster, 77-5605
 - Histological Study, 77-5605

Propionitrile, 3-Amino-

- Breast Neoplasms
- Collagen, 77-5983

Prostaglandins E

- Virus, Moloney Murine Sarcoma
- Neoplasms, Experimental, 77-5746

Prostaglandins F

- Virus, Moloney Murine Sarcoma
- Neoplasms, Experimental, 77-5746

Prostate

- Cell Division
- Tissue Culture, 77-5915

Prostatic Neoplasms

- Adenocarcinoma
 - Virus-Like Particles, 77-5852
- Adenoma
 - Tissue Culture, 77-5915
- Carcinoma
 - Tissue Culture, 77-5915
- Cell Division
 - Tissue Culture, 77-5915
- Virus-Like Particles
 - Ultrastructural Study, 77-5852

Proteins

- Benz(a)anthracene, 7,12-Dimethyl-
 - Liver, Rat, 77-5574
- Benzo(a)pyrene
 - Binding, 77-5565
- Cell Membrane
 - Isolation and Characterization, 77-5893
- Cell Transformation, Neoplastic
 - Cell Membrane, 77-5748, 77-5893
- Chromosomes
 - Antigens, Neoplasm, 77-5664
- Photochemistry
 - Ultraviolet Rays, 77-5420

Psoralen, 8-Methoxy-

- Chromosome Aberrations
 - Lymphocytes, 77-5672
- DNA
 - Binding, 77-5668
 - Photoproducts, 77-5671
- Skin Pigmentation
 - Ultrastructural Study, 77-5669
- Ultraviolet Rays
 - Cells, Cultured, 77-5668
 - DNA, 77-5671
 - Epidermis, Mouse, 77-5671

- Psoralen, 8-Methoxy- (cont'd)**
 Phototoxic Effect, 77-5670
 Skin, Mouse, 77-5670
 Skin Pigmentation, 77-5669
- Purine, 2-Amino-6-methoxy-**
 Hydrazine, 1,2-Dimethyl-
 DNA, 77-5503
- Purine-6-thiol**
 Exonucleases
 Enzymatic Activity, 77-5535
- Putrescine**
 Bladder
 Cells, Cultured, 77-5976
- 3,5-Pyrazolidinedione, 4-Butyl-1,2-diphenyl-**
 Gastric Mucosa
 Glycoproteins, Review, 77-5451
- Pyrene**
 Cells, Cultured
 Chromosome Aberrations, 77-5631
 Deuterium
 Synthesis, 77-5567
 Fish
 Tissue Concentrations, 77-5549
 Liver Neoplasms
 Transplacental Carcinogenesis, 77-5550
 Lung Neoplasms
 Adenoma, 77-5550
 Mammary Neoplasms, Experimental
 Transplacental Carcinogenesis, 77-5550
 Transplacental Carcinogenesis
 Mouse, 77-5550
- Pyridine, 2-(2-((Dimethylamino)ethyl)-2-thenylamino)-**
 Nitrous Acid, Sodium Salt
 Carcinogenic Potential, Rat, 77-5602
- Pyridinium, 3-(Aminocarbonyl)-1-methyl-**
 Acetamide, *N*-Fluoren-2-yl-
 Metabolism, Rat, 77-5467
- 2-Pyridone-5-carboxamide, 1-Methyl-**
 Acetamide, *N*-Fluoren-2-yl-
 Metabolism, Rat, 77-5467
- 4-Pyridone-5-carboxamide, 1-Methyl-**
 Acetamide, *N*-Fluoren-2-yl-
 Metabolism, Rat, 77-5467
- Pyrrolidine, 1-Nitroso-**
 Bronchi
 DNA, Binding, 77-5603
 Metabolism, 77-5603
- Quinoline, 4-Nitro-, 1-Oxide**
 Cells, Cultured
 Chromosome Aberrations, 77-5631
 Metabolism, 77-5625
 Chromosome Aberrations
 Cells, Cultured, 77-5629
 Tongue Neoplasms
 Croton Oil, 77-5624
 Hamster, 77-5624
 Papilloma, 77-5624
 Precancerous Conditions, 77-5624
 Virus, C-Type RNA Tumor
 Cell Transformation, Neoplastic, 77-5583
 Virus, Rous Sarcoma
 DNA Repair, 77-5703
- Quinoline-1-oxide, 4-Nitro-**
 DNA
 Mitochondria, 77-5623
- Radiation**
 Cell Differentiation
 Carcinogenesis Model, Review, 77-5432
 DNA
 Carcinogenesis Model, Review, 77-5432
- Radiation Chimera**
 Sarcoma, Yoshida
 Immune Response, 77-5876
- Radiation, Ionizing**
 Aging
 Capillaries, 77-5692
 Alanine
 Mutagenic Activity, 77-5649
Aspergillus nidulans
 Mutagenic Activity, 77-5651
 Ataxia Telangiectasia
 DNA Repair, 77-5433
 Breast Neoplasms
 Case Report, 77-5689
 Epidemiology, 77-5457, 77-5694
 Cells, Cultured
 Azaguanine Resistance, 77-5652
 Mutagenic Activity, 77-5649, 77-5652, 77-5681
 Chromosome Aberrations
 Dose-Response Study, 77-5650, 77-5696
 Review, 77-5435
Vicia faba, 77-5696
 Chromosome Abnormalities
Vicia faba, 77-5696
 Cold
 Thyroid Gland, 77-5686
 DNA Repair
 Cells, Cultured, 77-5673
 Mouse, 77-5674
 Hemangioendothelioma
 Mouse, 77-5655
 Interferon
 Cell Division, 77-5684
 Cell Transformation, Neoplastic, 77-5684
 Kidney Neoplasms
 Carcinoma, 77-5690
 Leukemia
 Epidemiology, 77-5682
 B-Lymphocytes, 77-5663
 T-Lymphocytes, 77-5663
 Mouse, 77-5655
 Mutagenic Activity, 77-5649
 Lung Neoplasms
 Adenocarcinoma, 77-5667
 Carcinoma, Bronchogenic, 77-5667
 Carcinoma, Epidermoid, 77-5667
 Histological Study, 77-5667
 Lymphocyte Transformation
 Chromosome Aberrations, 77-5650
 Lymphocytes
 Chromosome Aberrations, 77-5650
 Lymphoma
 Mouse, 77-5655
 Mutagenic Activity
 Lung Fibroblasts, Dose-Response Study, 77-5652
 Nephroblastoma
 Irradiation, Fetal, 77-5683
 Neuroblastoma

Radiation, Ionizing (cont'd)

- Irradiation, Fetal, 77-5683
- Pathology
 - Epidemiology, 77-5691
- Plant Agglutinins
 - Lymphocytes, 77-5650
- Progeria
 - DNA Repair, 77-5433
- Safety
 - Radiotherapy Dosage, 77-5695
- Sarcoma, Osteogenic
 - Antigens, Neoplasm, 77-5664
 - Case Report, 77-5654
 - Mouse, 77-5655
- Spinal Neoplasms
 - Sarcoma, Osteogenic, 77-5653
- Stomach Neoplasms
 - Epidemiology, 77-5693
- Testicular Neoplasms
 - Leydig Cell Tumor, 77-5685
- Thyroid Gland
 - Thyrotropin, 77-5686
 - Thyroxine, 77-5686
- Thyroid Gland Function Tests
 - Thyrotropin, 77-5686
- Thyroid Neoplasms
 - Carcinoma, 77-5687
 - Epidemiology, 77-5687
 - Epidemiology, Israel, 77-5688
- Uridine, 5-Bromo-2'-deoxy-
 - Mutagenic Activity, 77-5649

Radon

- Lung Neoplasms
 - Carcinoma, Epidermoid, 77-5419
 - Epidemiology, Review, 77-5419

Rauwolfia

- Breast Neoplasms
 - Epidemiology, 77-5529

Receptors, Hormone

- Breast Neoplasms
 - Carcinoma, 77-5918
- Leukemia, Lymphocytic
 - Lymphocytes, 77-5997

Respiratory System

- Carbenoxolone
 - Mucosal Glycoproteins, Review, 77-5452

Respiratory Tract Neoplasms

- Arsenic Trioxide
 - Occupational Hazard, 77-5636
- 2-Propen-1-amine, *N*-Nitroso-*N*-2-propenyl-
 - Dose-Response Study, Hamster, 77-5605
 - Histological Study, 77-5605

Reticulosarcoma

- see* Sarcoma, Reticulum Cell

Retinoblastoma

- Ethnic Groups
 - Epidemiology, 77-5458
- Histocompatibility Antigens
 - Epidemiology, 77-5879
- Histological Study
 - Review, 77-5445

Retinoic Acid

- Guanidine, 1-Methyl-3-nitro-1-nitroso-

Retinoic Acid (cont'd)

- Hyperplasia, 77-5620

Retinol

- Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-
 - Cytochrome P-450, 77-5492

Retinol Acetate

- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Hyperplasia, 77-5620

Retinyl Methyl Ether

- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Hyperplasia, 77-5620

Retronecine, 3,8-Didehydro-

- Cysteine
 - Binding, 77-5505
- Glutathione
 - Binding, 77-5505
- Monocrotaline
 - Carcinogenic Metabolite, 77-5505

Reverse Transcriptase

- Leukemia
 - Bone Marrow Cells, 77-5849
- Neoplasms, Vascular Tissue
 - Spleen, 77-5848
- Uridine, 5-Bromo-2'-deoxy-
 - Liver, Rat, 77-5749
- Virus, Herpes Simplex 1
 - Cell Transformation, Neoplastic, 77-5812
- Virus, Herpes Simplex 2
 - Cell Transformation, Neoplastic, 77-5812
- Virus, Mason-Pfizer Monkey
 - Antibody Specificity, 77-5777
 - Antigenic Determinants, 77-5777
 - Dexamethasone, 77-5775
 - Isolation and Characterization, 77-5777
 - Uridine, 2'-Deoxy-5-iodo-, 77-5775
- Virus, Murine Leukemia
 - Actinomycin D, 77-5741
 - Isolation and Characterization, 77-5741
 - RNA, Viral, 77-5741
- Virus, Rauscher Murine Leukemia
 - Antibodies, Viral, 77-5741
- Virus, RNA Tumor
 - DNA, Viral, 77-5709
- Virus Rous Sarcoma
 - RNA Replication, 77-5700
 - Virus, Avian Myeloblastosis, 77-5700
- Virus, Simian Sarcoma-Associated
 - Enzymatic Activity, 77-5778

Rhabdomyosarcoma

- Blood Proteins
 - Immune Response, 77-5863
- Cholanthere, 3-Methyl-
 - Mouse, 77-5863
- T-Lymphocytes
 - Immune Response, 77-5863
- Nickel
 - Rat, 77-5635

Ribonuclease

- Virus Rous Sarcoma
 - RNA Replication, 77-5700
 - Virus, Avian Myeloblastosis, 77-5700

Ribosomes

- Cholanthere, 3-Methyl-

Ribosomes (cont'd)

Skin, 77-5587

RNA

Benz(a)anthracene

Coliphages, 77-5545

Benz(a)anthracene, 5,6-Dihydro-5,6-epoxy-

Coliphages, 77-5545

Benz(a)anthracene, 7,12-Dimethyl-

Coliphages, 77-5545

Benz(a)anthracene, 12-Methyl-7-oxiranyl-

Coliphages, 77-5545

Benzene

Cell Nucleus, 77-5551

Benzo(a)pyrene

Binding, 77-5557, 77-5565, 77-5568

Cell Nucleus, 77-5551

Coliphages, 77-5545

DNA, 77-5557

HeLa Cells

Ultraviolet Rays, 77-5838

Phenanthrene

Coliphages, 77-5545

Polycyclic Hydrocarbons

Coliphages, 77-5545

Sarcoma

Cell Transformation, Neoplastic, 77-5704

RNA, Messenger

DNA, Viral

DNA-RNA Hybridization, 77-5834

Globin

DNA-RNA Hybridization, 77-5734

HeLa Cells

Ultraviolet Rays, 77-5838

Immunoglobulins

DNA-RNA Hybridization, 77-5989

Plasmacytoma

DNA-RNA Hybridization, 77-5989

Virus, Adeno 2

Base Sequence, 77-5833

DNA-RNA Hybridization, 77-5804, 77-5830
77-5832

DNA, Viral, 77-5804, 77-5830, 77-5834

Models, Theoretical, 77-5833

Virus, Friend Murine Leukemia

DNA-RNA Hybridization, 77-5734

Virus, SV40

Antigenic Determinants, 77-5790

Isolation and Characterization, 77-5787

RNA Polymerase

Virus, Herpes Simplex 1

Cells, Cultured, 77-5813

Virus, Murine Leukemia

Cells, Cultured, 77-5763

RNA Replication

Aging

Cells, Cultured, 77-5988

Embryo, Mouse, 77-5988

Virus Rous Sarcoma

Reverse Transcriptase, 77-5700

Ribonuclease, 77-5700

RNA, Transfer

Mutagenic Activity

Models, Theoretical, 77-5633

RNA, Transfer, Methyltransferases

Benz(a)anthracene, 7,12-Dimethyl-

Liver, Rat, 77-5574

RNA, Viral

Carcinoma

Virus, Feline Leukemia, 77-5715

Virus, RD-114, 77-5715

HeLa Cells

Ultraviolet Rays, 77-5838

Lymphoma

Virus, Feline Leukemia, 77-5715

Virus, RD-114, 77-5715

Neoplasms, Vascular Tissue

Spleen, 77-5848

Sarcoma

Virus, Feline Leukemia, 77-5715

Virus, RD-114, 77-5715

Virus, Adeno 2

Abundance Classes, 77-5832

DNA-RNA Hybridization, 77-5832

Isolation and Characterization, 77-5831

Transcription, Genetic, 77-5831

Ultraviolet Rays, 77-5838

Virus, D-Type RNA Tumor

Isolation and Characterization, 77-5780

Virus, Friend Murine Leukemia

DNA-RNA Hybridization, 77-5734

Isolation and Characterization, 77-5733

Virus, Leukemia

Isolation and Characterization, 77-5733

Virus, Mason-Pfizer Monkey

DNA-RNA Hybridization, 77-5776, 77-5780

Virus, Murine Leukemia

Gel Electrophoresis, 77-5768

Mice, AKR, 77-5768

Oligonucleotides, 77-5768

Reverse Transcriptase, 77-5741

Virus, Rous-Associated

Cells, Cultured, 77-5705

Virus, Rous Sarcoma

Cells, Cultured, 77-5705

DNA-RNA Hybridization, 77-5700

Isolation and Characterization, 77-5705

Virus, Spleen Focus-Forming

Isolation and Characterization, 77-5733

Virus, SV40

DNA-RNA Hybridization, 77-5786

Saccharomyces cerevisiae

Aflatoxin B1

Mutagenic Activity, 77-5511

Saccharomycopsis lipolytica

Nitrous Acid

1-Butanamine, *N*-Butyl-*N*-nitroso-, 77-5604Diethylamine, *N*-Nitroso-, 77-5604Dimethylamine, *N*-Nitroso-, 77-5604Dipentylamine, *N*-Nitroso-, 77-56041-Hexanamine, *N*-Hexyl-*N*-nitroso-, 77-5604Morpholine, *N*-Nitroso-, 77-5604

Piperidine, 1-Nitroso-, 77-5604

Safrole

see Benzene, 4-Allyl-1,2-(methylenedioxy)-

Salicylic Acid Acetate

see Benzoic Acid, 2-(Acetyloxy)-

Salivary Gland Neoplasms

- Asbestos
Epidemiology, 77-5955

Salmonella typhimurium

- Acetamide, *N*-Fluorenyl-2-yl-
Gastrointestinal System, Rat, 77-5473
Revertants, Germ-Free Rat, 77-5473
- Aniline
Mutagenic Activity, 77-5479
- Biphenyl, 4-Nitro-
Gastrointestinal System, Rat, 77-5473
Revertants, Germ-Free Rat, 77-5473
- 4-Biphenylamine, 3,2'-Dimethyl-
Gastrointestinal System, Rat, 77-5473
Revertants, Germ-Free Rat, 77-5473
- Butane, 1,2-Epoxy-
Mutagenic Activity, 77-5488
- Ethane, Azoxy-
Gastrointestinal System, Rat, 77-5473
Revertants, Germ-Free Rat, 77-5473
- Ethylene Oxide
Mutagenic Activity, 77-5489
- Ethylene, Trichloro-
Mutagenic Activity, 77-5488
- 9*H*-Fluorene, 2-Nitro-
Gastrointestinal System, Rat, 77-5473
Revertants, Germ-Free Rat, 77-5473
- Nitrous Acid
Mutagenic Activity, 77-5601
- Norharman
Mutagenic Activity, 77-5479
- Propane, 1-Chloro-2,3-epoxy-
Mutagenic Activity, 77-5488
- o*-Toluidine
Mutagenic Activity, 77-5479
- Water Pollution
Mutagenic Activity, 77-5494

Sarcoma

- Antibodies, Neoplasm
Mouse, 77-5886
- Antigens, Neoplasm
Immune Response, 77-5854
- Brain Neoplasms
Genetics, 77-5442
- Carcinoembryonic Antigen
Immunologic Technics, 77-5869
- Cells, Cultured
Glucosaminidase, 77-5573
Lysosomes, 77-5573
- Cells, Culutred
Glucosaminidase, 77-5573
Lysosomes, 77-5573
- Cholanthrene, 3-Methyl-
Carcinoembryonic Antigen, 77-5869
Chromosomes, 77-5909
Immune Response, 77-5854, 77-5855, 77-5886
Immunologic Technics, 77-5869
Mouse, 77-5886
Teratoid Tumor, 77-5869
- Chromosomes
Cell-Cycle Kinetics, 77-5909
- Immune Response
Rat, 77-5874
- Macrophages
Immune Response, 77-5874
- Neoplasms

Sarcoma (cont'd)

- Genetics, 77-5442
- Neoplasms, Multiple Primary
Genetics, 77-5442
- Nickel
Rat, 77-5635
- RNA
Cell Transformation, Neoplastic, 77-5704
- Teratoid Tumor
Antigenic Determinants, 77-5869
- Uterine Neoplasms
Diagnosis and Prognosis, 77-5910
Hydrazine, 1,2-Dimethyl-, 77-5500
- Virus, Feline Leukemia
RNA, Viral, 77-5715
Viral Proteins, 77-5715
- Virus, Kirsten Murine Sarcoma
Cells, Cultured, 77-5749
- Virus, Moloney Murine Sarcoma
Immune Response, 77-5874
- Virus, RD-114
RNA, Viral, 77-5715
Viral Proteins, 77-5715
- Virus, Rous Sarcoma
Cell Transformation, Neoplastic, 77-5704
Glucosaminidase, 77-5573
Lysosomes, 77-5573
- Virus, SV40
Histocompatibility Antigens, 77-5885
- Sarcoma 180, Crocker**
T-Lymphocytes
Immune Response, 77-5862
- Sarcoma, Ewing's**
Ethnic Groups
Epidemiology, 77-5458
- Sarcoma, Mast Cell**
Antibody Formation
Inhibitory Factor, Culture Supernatant, 77-5861
Cells, Cultured
Immunosuppression, 77-5861
- Sarcoma, Osteogenic**
Antigens, Neoplasm
Isolation and Characterization, 77-5882
Ethnic Groups
Epidemiology, 77-5458
Mouse
Histological Study, 77-5655
Neoplasms, Radiation-Induced
C-Type Particles, 77-5764
Virus, C-Type RNA Tumor, 77-5764
Radiation, Ionizing
Antigens, Neoplasm, 77-5664
Case Report, 77-5654
Mouse, 77-5655
Spinal Neoplasms
Case Report, 77-5653
Radiation, Ionizing, 77-5653
- Sarcoma, Reticulum Cell**
Intestinal Neoplasms
Hydrazine, 1,2-Dimethyl-, 77-5500
Phosphoric Acid, Titanium Salt
Rat, 77-5644
- Sarcoma, Yoshida**
Histocompatibility Antigens

- Sarcoma, Yoshida (cont'd)**
 Immune Response, 77-5876
 B-Lymphocytes
 Immune Response, 77-5876
 T-Lymphocytes
 Immune Response, 77-5876
 Radiation Chimera
 Immune Response, 77-5876
- Sebaceous Gland Neoplasms**
 Cells, Cultured
 Cell Differentiation, 77-5975
 Lipids
 Cell Differentiation, 77-5975
- Selenium**
 Liver Neoplasms
 Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-, 77-5480
- Seminoma**
 see Disgerminoma
- Serum Albumin**
 Estradiol
 Binding, 77-5519
 4,4'-Stilbenediol, α,α' -Diethyl-
 Binding, 77-5519
- Silver**
 DNA Replication
 Carcinogenic Activity, 77-5634
 Mutagenic Activity, 77-5634
- Skin**
 Cholanthrene, 3-Methyl-
 Cell Transformation, Neoplastic, 77-5585
 Histological Study, 77-5587
 Mouse, 77-5587
 Ribosomes, 77-5587
 Ultrastructural Study, Mouse, 77-5585
- Skin Neoplasms**
 Arsenic
 Chromosome Aberrations, 77-5640
 Epidemiology, Taiwan, 77-5638
 Water Pollution, 77-5638
 Benzo(a)pyren-11-ol
 Mouse, 77-5560
 Benzo(a)pyren-2-ol
 Mouse, 77-5560
 Benzo(a)pyrene
 Mouse, 77-5560
 Benzo(a)pyrene, (+)-*trans*-7,8-Dihydroxy-7,8-dihydro-
 Mouse, 77-5561
 5,6-Benzoflavone
 Benz(a)anthracene, 7,12-Dimethyl-, 77-5548
 Cholanthrene, 3-Methyl-, 77-5548
 Dibenz(a,h)anthracene, 77-5548
 7,8-Benzoflavone
 Benz(a)anthracene, 7,12-Dimethyl-, 77-5548
 Cholanthrene, 3-Methyl-, 77-5548
 Dibenz(a,h)anthracene, 77-5548
 Carcinoma
 Arsenic, 77-5637
 Fluclorolone Acetonide, 77-5540
 Fluocinolone Acetonide, 77-5540
 12-*O*-Tetradecanoylphorbol-13-acetate, 77-5540
 Carcinoma, Basal Cell
 Xeroderma Pigmentosum, 77-5434
 Carcinoma, Epidermoid
- Skin Neoplasms (cont'd)**
 Xeroderma Pigmentosum, 77-5434
 Fibrosarcoma
 Case Report, 77-5926
 Ultrastructural Study, 77-5926
 Fish
 Epidemiology, Review, 77-5407
 Melanoma
 Epidemiology, 77-5458, 77-5942
 Ultraviolet Rays, 77-5942
 Xeroderma Pigmentosum, 77-5434
 Papilloma
 Fluclorolone Acetonide, 77-5540
 Fluocinolone Acetonide, 77-5540
 12-*O*-Tetradecanoylphorbol-13-acetate, 77-5540
 Peroxyacetyl Nitrate
 Oxidants, Chemical, Review, 77-5418
 12-*O*-Tetradecanoylphorbol-13-acetate
 Mouse, 77-5561
 Ultraviolet Rays
 Mouse, 77-5678
 Vascular Diseases
 Epidemiology, Taiwan, 77-5638
 Water Pollution
 Fish, 77-5407
- Smoking**
 Aryl Hydrocarbon Hydroxylases
 Genetics, Mouse, 77-5592
 Liver, Lung, Mouse, 77-5592
 Lymphocytes, 77-5591
 Macrophages, 77-5591
 Bladder Neoplasms
 Epidemiology, 77-5416
 Esophageal Neoplasms
 Epidemiology, 77-5416, 77-5459
 Kidney Neoplasms
 Aryl Hydrocarbon Hydroxylases, 77-5589
 Laryngeal Neoplasms
 Epidemiology, 77-5416
 Liver Neoplasms
 Epidemiology, 77-5943
 Liver Cirrhosis, 77-5943
 Lung
 Acid Phosphatase, 77-5594
 Biochemical Study, Rat, 77-5594
 Collagen, 77-5594
 Elastin, 77-5594
 Glucuronidase, 77-5594
 Hexosamines, 77-5594
 Histological Study, 77-5595
 Lung Neoplasms
 Epidemiology, 77-5416, 77-5417
 Mesothelioma, 77-5952
 Macrophages
 Ultrastructural Study, 77-5593
 Mouth Neoplasms
 Epidemiology, 77-5416, 77-5459, 77-5943
 Pancreatic Neoplasms
 Epidemiology, Review, 77-5449
 Polycyclic Hydrocarbons
 Condensate, Cigarette, 77-5596
 Ureteral Neoplasms
 Aryl Hydrocarbon Hydroxylases, 77-5589
- Sodium Arsenate**
 see Arsenic Acid, Sodium Salt

- Somatotropin**
Virus Replication
Cells, Cultured, 77-5754
- Spermidine**
Bladder
Cells, Cultured, 77-5976
- Spermine**
Bladder
Cells, Cultured, 77-5976
- Spinal Neoplasms**
Sarcoma, Osteogenic
Case Report, 77-5653
Radiation, Ionizing, 77-5653
- Spleen**
Neoplasms, Vascular Tissue
Reverse Transcriptase, 77-5848
RNA, Viral, 77-5848
Virus-Like Particles, 77-5848
Virus, Moloney Murine Leukemia
Immune Response, 77-5860
Immunosuppression, 77-5860
- Splenic Neoplasms**
Benzene, Hexachloro-
Hemangioendothelioma, 77-5483
- Sprue**
Abdominal Neoplasms
Lymphoma, 77-5894
- Sterigmatocystin**
Aflatoxin B1
Mutagenic Activity, Biosynthetic Intermediates
77-5510
- 4,4'-Stilbenediol, α, α' -Diethyl-**
Gynecologic Neoplasms
Histological Study, 77-5518
Metabolism
Mouse, 77-5517
Serum Albumin
Binding, 77-5519
Vagina
Cytology, 77-5520
Vaginal Neoplasms
Adenocarcinoma, 77-5445
Virus, Murine Mammary Tumor
Antigens, Viral, 77-5753
- Stomach Neoplasms**
Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-
Carcinoma, Epidermoid, 77-5462
Food Preservatives, 77-5462
Mouse, 77-5462
Adenocarcinoma
Histological Study, 77-5621
Asbestos
Water Pollution, 77-5957
Carcinoma
Ataxia Telangiectasia, 77-5440
Diet
Epidemiology, 77-5460
Epidemiology, Turkey, 77-5939
Nitrosamines, 77-5460
Review, 77-5460
Epidemiology
Statistical Analysis, 77-5938
Nitrous Acid
- Stomach Neoplasms (cont'd)**
Food, 77-5601
Radiation, Ionizing
Epidemiology, 77-5693
Tars
Epidemiology, Turkey, 77-5939
Tea
Epidemiology, Turkey, 77-5939
- Strontium Radioisotopes**
Thyroid Neoplasms
Adenoma, 77-5665
Carcinoma, 77-5665
Cesium Radioisotopes, 77-5665
- Styrene**
Adipose Tissue
Metabolism, Review, 77-5495
Occupational Hazard
Metabolism, Review, 77-5495
- Succinate Dehydrogenase**
Actinomycin D
Enzymatic Activity, 77-5546
Carbon Tetrachloride
Enzymatic Activity, 77-5546
Cholanthrene, 3-Methyl-
Enzymatic Activity, 77-5546
Liver, 77-5546
Dibenz(a,h)anthracene
Enzymatic Activity, 77-5546
Lung Neoplasms
Enzymatic Activity, 77-5656
- Sulphydryl Compounds**
Cytochrome P-448
Metabolism, 77-5554
- Sulfuric Acid, Dimethyl Ester**
Chromosome Aberrations
Cells, Cultured, 77-5629
- Tars**
Esophageal Neoplasms
Tea, 77-5939
Stomach Neoplasms
Epidemiology, Turkey, 77-5939
- Teratocarcinoma**
see Teratoid Tumor
- Teratoid Tumor**
Cell Differentiation
Ultrastructural Study, 77-5914
Neoplasm Metastasis
Ultrastructural Study, 77-5914
Sarcoma
Antigenic Determinants, 77-5869
Cholanthrene, 3-Methyl-, 77-5869
Virus, SV40
Cells, Cultured, 77-5793
- Teratoma**
see Teratoid Tumor
- Testicular Neoplasms**
Disgerminoma
Case Report, 77-5690
Radiation, Ionizing
Leydig Cell Tumor, 77-5685
- Testosterone**
Breast Neoplasms

- Testosterone (cont'd)**
 Cell Survival, 77-5996
 Mammary Neoplasms, Experimental
 Cell Survival, 77-5996
 Vagina
 Cytology, 77-5520
- 12-*O*-Tetradecanoylphorbol-13-acetate**
 Cells, Cultured
 Mutagenic Activity, 77-5536, 77-5537
 Cholanthrene, 3-Methyl-
 DNA Replication, 77-5539
 DNA Replication
 Cells, Cultured, 77-5539
 Phorbol Esters
 Metabolism, Mouse, 77-5538
 Skin Neoplasms
 Carcinoma, 77-5540
 Mouse, 77-5561
 Papilloma, 77-5540
- 1-Tetralone, 4-Hydroxy-**
 Naphthalene
 Carcinogenic Metabolite, 77-5541
 Oxidation
 Carcinogenic Metabolite, 77-5541
- Thorium Dioxide**
 Angiosarcoma
 Epidemiology, 77-5945
- Thymidine Kinase**
 Virus, Herpes Simplex 2
 Cells, Cultured, 77-5815
 DNA, Viral, 77-5815
- Thymoma**
 Urea, 1-Butyl-1-nitroso-
 Mouse, 77-5617
 Urea, Methyl Nitroso-
 Mouse, 77-5617
- Thyroid Gland**
 Radiation, Ionizing
 Cold, 77-5686
 Thyrotropin, 77-5686
 Thyroxine, 77-5686
- Thyroid Neoplasms**
 Adenocarcinoma
 Hamartoma, 77-5439
 Adenoma
 Calcium Radioisotopes, 77-5665
 Cesium Radioisotopes, 77-5665
 Strontium Radioisotopes, 77-5665
 Benzene, Hexachloro-
 Adenoma, 77-5483
 Carcinoma
 Calcium Radioisotopes, 77-5665
 Radiation, Ionizing, 77-5687
 Strontium Radioisotopes, 77-5665
 Genetics
 Review, 77-5447
 Radiation, Ionizing
 Epidemiology, 77-5687
 Epidemiology, Israel, 77-5688
 Strontium Radioisotopes
 Cesium Radioisotopes, 77-5665
- Thyrotropin**
 Radiation, Ionizing
- Thyrotropin (cont'd)**
 Thyroid Gland, 77-5686
 Thyroid Gland Function Tests, 77-5686
- Thyroxine**
 Radiation, Ionizing
 Thyroid Gland, 77-5686
- Tobacco**
 Carcinogenic Potential
 Mouse, 77-5597
 Esophageal Neoplasms
 Epidemiology, 77-5459
 Mouth Neoplasms
 Alcohol Drinking, 77-5416
 Epidemiology, 77-5459
 Phenols
 Isolation and Characterization, Pyrolyzate, 77-5596
 Polycyclic Hydrocarbons
 Isolation and Characterization, Pyrolyzate, 77-5596
- o*-Toluidine**
Salmonella typhimurium
 Mutagenic Activity, 77-5479
- o*-Toluidine, (4-*o*-tolylazo)-**
 Antigens
 Liver, 77-5482
- Tongue Neoplasms**
 Papilloma
 Quinoline, 4-Nitro-, 1-Oxide, 77-5624
 Quinoline, 4-Nitro-, 1-Oxide
 Croton Oil, 77-5624
 Hamster, 77-5624
 Precancerous Conditions, 77-5624
- Trachea**
 Benzo(a)pyrene, 4,5-Dihydro-4,5-dihydroxy-
 Metabolism, Hamster, 77-5563
- Transcription, Genetic**
 Virus, Adeno 2
 RNA, Viral, 77-5831
- Transformation, Genetic**
 Virus, Adeno 3
 DNA, Viral, 77-5841
 Virus, Adeno 7
 DNA, Viral, 77-5841
- Transplantation, Heterologous**
 Leukemia, Myelocytic
 Chromosomes, Human, 21-22, 77-5858
 Histological Study, 77-5858
 Mouse, Nude, 77-5858
- Transplantation, Homologous**
 Leukemia, Myelocytic
 Neoplasm Metastasis, 77-5895
- Triazene, 3,3-Dimethyl-1-(*m*-pyridyl)-**
 Chromosome Aberrations
Drosophila melanogaster, 77-5401
- s*-Triazin-2(1*H*)-one, 4-Amino-1- β -*D*-ribofuranosyl-**
 Cells, Cultured
 Histological Study, 77-5532
- 1,1,1-Trichloro-2,3-propene Oxide**
see Propane, 1,2-Epoxy-3,3,3-trichloro-

Trichoepithelioma

see Skin Neoplasms

Trimethylamine, *N*-Oxide

Nitrous Acid, Sodium Salt

Carcinogenic Potential, Rat, 77-5602

4,5',8-Trimethylpsoralen

see 7*H*-Furo[3,2-*g*](1)benzopyran-7-one, 2,5,9-Trimethyl-

Tyrosine

Cycloheximide

Melanin, 77-5986

Melanoma

Melanin, 77-5986

Urea, 1-Phenyl-2-thio-

Melanin, 77-5986

Ultraviolet Rays

Antioxidants

Carcinogenic Activity, Review, 77-5421

Caffeine

Mutagenic Activity, 77-5679

Cells, Cultured

Mutagenic Activity, 77-5679, 77-5680, 77-5681

Chromosome Aberrations

Lymphocytes, 77-5672

Dietary Fats

Carcinogenic Activity, Review, 77-5421

DNA

Binding, Acridine, 77-5676

Epidermal Cells, 77-5676

DNA Repair

Carcinogenic Activity, Review, 77-5421

Cells, Cultured, 77-5675

Escherichia coli

DNA Repair, 77-5677

Fibrosarcoma

Immune Response, 77-5856

Heat

DNA Denaturation, Synergistic Effect, 77-5676

HeLa Cells

RNA, 77-5838

RNA, Messenger, 77-5838

RNA, Viral, 77-5838

Immune Response

Mouse, 77-5856, 77-5872

Immunosuppression

Carcinogenic Activity, Review, 77-5421

Lymphocytes

Immune Response, 77-5872

Macrophages

Immune Response, 77-5872

Peroxyacetyl Nitrate

Co-carcinogenic Effect, Review, 77-5418

Photochemistry

Nucleic Acids, 77-5420

Proteins, 77-5420

Radiation-Sensitizing Agents, 77-5420

Psoralen, 8-Methoxy-

Cells, Cultured, 77-5668

DNA, 77-5671

Epidermis, Mouse, 77-5671

Phototoxic Effect, 77-5670

Skin, Mouse, 77-5670

Skin Pigmentation, 77-5669

Skin Neoplasms

Melanoma, 77-5942

Mouse, 77-5678

Ultraviolet Rays (cont'd)

Skin Pigmentation

Ultrastructural Study, 77-5669

Virus, Adeno 2

RNA, Viral, 77-5838

Virus, Moloney Murine Sarcoma-Leukemia

Temperature Sensitive Mutants, 77-5743

Virus, Rous Sarcoma

DNA Repair, 77-5703

Virus, SV40

DNA Replication, 77-5795

Mutagenic Activity, 77-5795

Xeroderma Pigmentosum

DNA Repair, 77-5433, 77-5434

Urea

Bladder Neoplasms

Carcinoma, 77-5978

Urea, 1-Butyl-1-nitroso-

Leukemia, Lymphoblastic

Mouse, 77-5617

Thymoma

Mouse, 77-5617

Urea, *N,N*-Dimethyl-*N*-phenyl-

Nitrous Acid, Sodium Salt

Carcinogenic Potential, Rat, 77-5602

Urea, Ethyl Nitroso-

Brain Neoplasms

Glioma, 77-5613

Cell Transformation, Neoplastic

Transplacental Carcinogenesis, 77-5615

Cells, Cultured

Fibrinolysis, 77-5612

Glioblastoma Multiforme

Histological Study, 77-5615

Glioma

Histological Study, 77-5615

Glycogenosis

Transplacental Carcinogenesis, 77-5614

Hepatoma

Glycogenosis, 77-5614

Precancerous Conditions, 77-5614

Transplacental Carcinogenesis, 77-5614

Nervous System Neoplasms

Rat, 77-5615

Neurilemmoma

Histological Study, 77-5615

Urea, Hydroxy-

DNA Polymerase

DNA Replication, 77-5758

Urea, Methyl Nitroso-

DNA Repair

Cells, Cultured, 77-5616

Leukemia, Lymphoblastic

Mouse, 77-5617

Lung

Cells, Cultured, 77-5619

Thymoma

Mouse, 77-5617

Urea, 1-Phenyl-2-thio-

Tyrosine

Melanin, 77-5986

- Ureteral Neoplasms**
 - Aryl Hydrocarbon Hydroxylases
 - Smoking, 77-5589
 - Carcinoma
 - Aryl Hydrocarbon Hydroxylases, 77-5589
- Urethral Neoplasms**
 - Carcinoma, Epidermoid
 - Case Report, 77-5916
 - Urethra Stricture, 77-5916
- Uridine, 5-Bromo-2'-deoxy-**
 - Cells, Cultured
 - Mutagenic Activity, 77-5632
 - Melanoma
 - Peptide Hydrolases, 77-5985
 - Nucleoproteins
 - DNA, Binding, 77-5984
 - Embryo, Rat, 77-5984
 - Radiation, Ionizing
 - Mutagenic Activity, 77-5649
 - Reverse Transcriptase
 - Liver, Rat, 77-5749
 - Virus-Like Particles
 - Liver, Rat, 77-5749
- Uridine, 2'-Deoxy-5-fluoro-**
 - DNA Polymerase
 - DNA Replication, 77-5758
- Uridine, 2'-Deoxy-5-iodo-**
 - Melanoma
 - Virus, Vesicular Stomatitis, 77-5853
 - Virus, Mason-Pfizer Monkey
 - Reverse Transcriptase, 77-5775
 - Virus Replication, 77-5775
- Uridine Diphosphate Sugars**
 - Benzo(a)pyrene
 - Aryl Hydrocarbon Hydroxylases, 77-5564
 - Metabolism, Liver, 77-5564
 - Oxidoreductases, 77-5564
- Urine**
 - Acetamide, *N*-Fluoren-2-yl-
 - Carcinogenic Metabolite, 77-5469
 - Virus, Polyoma, BK
 - Antigens, Viral, 77-5842
 - Virus, Polyoma, JC
 - Antigens, Viral, 77-5842
- Urogenital Neoplasms**
 - Carcinoma, Transitional Cell
 - Genetics, 77-5936
 - Ethylene, Chloro- Polymer
 - Epidemiology, 77-5946
 - Genetics
 - Case Report, 77-5936
 - Kidney Diseases
 - Genetics, 77-5936
 - Neoplasms, Multiple Primary
 - Genetics, 77-5936
 - Occupational Hazard
 - Epidemiology, 77-5946
- Uterine Neoplasms**
 - Adenocarcinoma
 - Diagnosis and Prognosis, 77-5910
 - Adenocarcinoma
 - Contraceptives, Oral, 77-5413
- Uterine Neoplasms (cont'd)**
 - Diagnosis and Prognosis, 77-5910
 - Adenoma
 - Diagnosis and Prognosis, 77-5910
 - Bromocriptine
 - Epidemiology, 77-5530
 - Carcinoma, Epidermoid
 - Diagnosis and Prognosis, 77-5910
 - Contraceptives, Oral
 - Review, 77-5413
 - Estrogens
 - Review, 77-5413
 - Genetics
 - Epidemiology, 77-5904
 - Hydrazine, 1,2-Dimethyl-
 - Phosphonic Acid, (2,2,2-Trichloro-1-hydroxyethyl)-
 - Dimethyl Ester, 77-5500
 - Sarcoma, 77-5500
 - Leiomyoma
 - Histological Study, 77-5912
 - Ultrastructural Study, 77-5912
 - Sarcoma
 - Diagnosis and Prognosis, 77-5910
- Vagina**
 - Estra-1,3,5(10)-triene-3,17-diol(17 β)-, 3-Benzoate
 - Cytology, 77-5520
 - Estra-1,3,5(10)-triene-3,17 β -diol, 17-Pentanoate
 - Cytology, 77-5520
 - Estradiol, Ethynyl-
 - Cytology, 77-5520
 - Estriol
 - Cytology, 77-5520
 - Estrogens
 - Cytology, 77-5520
 - 4,4'-Stilbenediol, α,α' -Diethyl-
 - Cytology, 77-5520
 - Testosterone
 - Cytology, 77-5520
- Vaginal Neoplasms**
 - Adenocarcinoma
 - 4,4'-Stilbenediol, α,α' -Diethyl-, 77-5445
- Vascular Diseases**
 - Arsenic
 - Epidemiology, Taiwan, 77-5638
 - Skin Neoplasms
 - Epidemiology, Taiwan, 77-5638
- Versicolorin A**
 - Aflatoxin B1
 - Mutagenic Activity, Biosynthetic Intermediates
 - 77-5510
- Versiconal Acetate**
 - Aflatoxin B1
 - Mutagenic Activity, Biosynthetic Intermediates
 - 77-5510
- Versiconal Hemiacetal Acetate**
 - Aspergillus parasiticus*
 - Biosynthesis, 77-5509
 - Mycotoxins
 - Biosynthesis, 77-5509
 - Phosphoric Acid, 2,2-Dichlorovinyl-, Dimethyl Ester
 - Biosynthesis, 77-5509
- Viral Proteins**
 - Burkitt's Lymphoma
 - Virus, Epstein-Barr, 77-5828

Viral Proteins (cont'd)

- Carcinoma**
 - Virus, Feline Leukemia, 77-5715
 - Virus, RD-114, 77-5715
- Lymphoma**
 - Virus, Feline Leukemia, 77-5715
 - Virus, RD-114, 77-5715
- Sarcoma**
 - Virus, Feline Leukemia, 77-5715
 - Virus, RD-114, 77-5715
- Virus, Adeno 2**
 - Isolation and Characterization, 77-5829
- Virus, Adeno 2 - SV40 Hybrid**
 - Intracellular Distribution, 77-5805
 - Isolation and Characterization, 77-5802
 - Ribosomes, Binding, 77-5805
 - Temperature Sensitive Mutants, 77-5835
 - Virus Replication, 77-5805
 - Virus, SV40, 77-5805
- Virus, Avian Sarcoma**
 - Isolation and Characterization, 77-5425
- Virus, C-Type RNA Tumor**
 - Isolation and Characterization, 77-5771, 77-5772
- Virus, Feline Leukemia**
 - Antigenic Determinants, 77-5716
 - Isolation and Characterization, 77-5716
- Virus, Gazdar Murine Sarcoma**
 - Isolation and Characterization, 77-5751
- Virus, Murine Leukemia**
 - Isolation and Characterization, 77-5725
- Virus, Murine Mammary Tumor**
 - Antigenic Determinants, 77-5757
- Virus, Polyoma**
 - Isolation and Characterization, 77-5762
 - Temperature Sensitive Mutants, 77-5762
- Virus, Rauscher Murine Leukemia**
 - Isolation and Characterization, 77-5725, 77-5726
 - 77-5728, 77-5772
- Virus, RD-114**
 - Isolation and Characterization, 77-5772
- Virus, Simian Sarcoma**
 - Isolation and Characterization, 77-5779
- Virus, Simian Sarcoma-Associated**
 - Isolation and Characterization, 77-5778
- Virus, SV40**
 - DNA, Viral, 77-5789
 - Virus Replication, 77-5789

Viral Vaccines

- Virus, Avian Leukosis**
 - Epidemiology, Review, 77-5424
- Virus, Epstein-Barr**
 - Epidemiology, Review, 77-5423
- Virus, Herpes Simplex 2**
 - Epidemiology, Review, 77-5423
- Virus, Marek's Disease Herpes**
 - Epidemiology, Review, 77-5424
- Virus, Abelson Murine Leukemia**
 - Plasmacytoma
 - Virus-Like Particles, A-Type, 77-5770
- Virus, C-Type RNA Tumor**
 - DNA-RNA Hybridization, 77-5770

Virus, Adeno

- Antigens, Viral**
 - Cells, Cultured, 77-5724
 - Immune Response, 77-5724

Virus, Adeno 2

- DNA Nucleotidyltransferases**
 - DNA Replication, 77-5840
 - Isolation and Characterization, 77-5840
- DNA Replication**
 - Isolation and Characterization, 77-5839
- DNA-RNA Hybridization**
 - Ultrastructural Study, 77-5834, 77-5837
- DNA, Viral**
 - DNA Replication, 77-5839
 - RNA, Messenger, 77-5830
 - Ultrastructural Study, 77-5829, 77-5837
- HeLa Cells**
 - DNA Nucleotidyltransferases, 77-5840
- RNA, Messenger**
 - Base Sequence, 77-5833
 - DNA-RNA Hybridization, 77-5804, 77-5830
 - 77-5832
 - DNA, Viral, 77-5804, 77-5834
 - Models, Theoretical, 77-5833
- RNA, Viral**
 - Abundance Classes, 77-5832
 - DNA-RNA Hybridization, 77-5832
 - Isolation and Characterization, 77-5831
 - Transcription, Genetic, 77-5831
 - Ultraviolet Rays, 77-5838
- Viral Proteins**
 - Isolation and Characterization, 77-5829

Virus, Adeno 3

- DNA, Viral**
 - Endonucleases, 77-5841
 - Transformation, Genetic, 77-5841
- Virus, Adeno 7**
 - DNA-RNA Hybridization, 77-5841

Virus, Adeno 5

- Burkitt's Lymphoma**
 - Antigens, Viral, 77-5828
 - Virus Replication, 77-5827
- DNA, Viral**
 - Ultrastructural Study, 77-5835
- Virus, Epstein Barr**
 - Virus Replication, 77-5827
- Virus Replication**
 - DNA, Viral, 77-5836

Virus, Adeno 7

- DNA, Viral**
 - Endonucleases, 77-5841
 - Transformation, Genetic, 77-5841
- Virus, Adeno 3**
 - DNA-RNA Hybridization, 77-5841

Virus, Adeno 12

- Neoplasms, Experimental**
 - Histological Study, 77-5803

Virus, Adeno 2 - SV40 Hybrid

- Antigens, Viral**
 - HeLa Cells, 77-5802
- Viral Proteins**
 - Intracellular Distribution, 77-5805
 - Isolation and Characterization, 77-5802
 - Ribosomes, Binding, 77-5805
 - Temperature Sensitive Mutants, 77-5835
 - Virus Replication, 77-5805
- Virus, SV40**
 - Viral Proteins, 77-5805

- Virus, Avian Leukosis**
 - Lymphoma
 - Epidemiology, Review, 77-5424
 - Viral Vaccines
 - Epidemiology, Review, 77-5424
- Virus, Avian Leukosis-Sarcoma**
 - Crosses, Genetic
 - DNA-RNA Hybridization, 77-5714
 - DNA, Viral
 - DNA-RNA Hybridization, 77-5714
 - Nucleotides, Pheasant, 77-5714
- Virus, Avian Myeloblastosis**
 - Virus Rous Sarcoma
 - Reverse Transcriptase, 77-5700
 - Ribonuclease, 77-5700
- Virus, Avian Reticuloendotheliosis**
 - Virus Replication
 - Isolation and Characterization, 77-5701
- Virus, Avian Sarcoma**
 - Antigens, Viral
 - Cell Transformation, Neoplastic, 77-5710
 - DNA, Viral
 - DNA-DNA Hybridization, 77-5712
 - Isolation and Characterization, 77-5712
 - Viral Proteins
 - Isolation and Characterization, 77-5425
 - Virus Replication
 - Isolation and Characterization, 77-5701
- Virus, Baboon**
 - Melanoma
 - Antibodies, Viral, 77-5810
- Virus, Baboon C-Type RNA Tumor**
 - Antigens, Viral
 - Antibodies, Neoplasm, 77-5891
- Virus, Bovine Adeno**
 - DNA, Viral
 - Isolation and Characterization, 77-5723
- Virus, Bovine Leukemia**
 - Antibodies, Viral
 - Epidemiology, 77-5719, 77-5721
 - Fetus
 - Virus Replication, 77-5722
 - Germ Cells
 - Vertical Transmission, 77-5722
 - Lymphosarcoma
 - Antigens, Neoplasm, 77-5883
 - Placenta
 - Vertical Transmission, 77-5722
 - Sheep
 - Vertical Transmission, 77-5722
 - Virus Replication
 - Ultrastructural Study, 77-5720
- Virus, C-Type RNA Tumor**
 - Cell Transformation, Neoplastic
 - Cholanthrene, 3-Methyl-, 77-5583
 - Quinoline, 4-Nitro-, 1-Oxide, 77-5583
 - Rat, 77-5583
 - Erythroleukemia
 - Isolation and Characterization, 77-5733
 - Glioblastoma Multiforme
 - Ultrastructural Study, 77-5766
 - Leukemia
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-5765
- Virus, C-Type RNA Tumor (cont'd)**
 - B-Lymphocytes
 - Antigens, Viral, 77-5769
 - Melanoma
 - Antibodies, Viral, 77-5810
 - Neoplasms, Radiation-Induced
 - Sarcoma, Osteogenic, 77-5764
 - Virus Replication, 77-5764
 - Reptiles
 - Isolation and Characterization, 77-5771
 - Viral Proteins
 - Isolation and Characterization, 77-5771, 77-5772
 - Virus, Abelson Murine Leukemia
 - DNA-RNA Hybridization, 77-5770
 - Virus, HEL-12
 - Virus Replication, 77-5811
 - Virus, Herpes Simplex 1
 - Virus Replication, 77-5812
 - Virus, Herpes Simplex 2
 - Virus Replication, 77-5812
 - Virus-Like Particles, A-Type
 - Antibodies, Viral, 77-5770
 - Virus, Mason-Pfizer Monkey
 - Virus Replication, 77-5775
- Virus, Chick Syncytial**
 - see Virus, Avian Reticuloendotheliosis
- Virus, D-Type Retra**
 - see Virus, D-Type RNA Tumor
- Virus, D-Type RNA Tumor**
 - Antigens, Viral
 - Cells, Cultured, 77-5851
 - Breast Neoplasms
 - Antigens, Viral, 77-5851
 - Cells, Cultured
 - DNA-RNA Hybridization, 77-5780
 - Isolation and Characterization
 - Monkey, 77-5780
 - RNA, Viral
 - Isolation and Characterization, 77-5780
 - Virus-Like Particles
 - Isolation and Characterization, Squirrel Monkey 77-5781
 - Placenta, 77-5781
- Virus, Epstein-Barr**
 - Antigens, Viral
 - Cells, Cultured, 77-5820, 77-5822
 - DNA Replication, 77-5821
 - Arginine
 - Antigens, Viral, 77-5821
 - Burkitt's Lymphoma
 - Antibodies, Viral, 77-5823
 - DNA, Viral, 77-5826
 - Epidemiology, 77-5457, 77-5825
 - Review, 77-5446
 - Viral Proteins, 77-5828
 - Cell Transformation, Neoplastic
 - Nucleic Acid Hybridization, 77-5826
 - Cells, Cultured
 - Ultrastructural Study, 77-5819
 - DNA, Viral
 - Cell Transformation, Neoplastic, 77-5826
 - Isolation and Characterization, 77-5826
 - Ultrastructural Study, 77-5818
 - Histocompatibility Antigens
 - T-Lymphocytes, 77-5877

- Virus, Epstein-Barr (cont'd)**
 - Immunity, Cellular, 77-5877
- Leukemia, Lymphoblastic**
 - DNA-DNA Hybridization, 77-5896
 - Receptors, Viral, 77-5878
- Nasopharyngeal Neoplasms**
 - Antibodies, Viral, 77-5823, 77-5824
 - Carcinoma, 77-5459, 77-5822, 77-5823, 77-5824 77-5934
 - Epidemiology, 77-5457
 - Immune Response, 77-5935
- Plant Agglutinins**
 - Antigens, Viral, 77-5821
- Viral Vaccines**
 - Epidemiology, Review, 77-5423
- Virus, Adeno 5**
 - Virus Replication, 77-5827
- Virus, Herpes Saimiri**
 - Antigenic Determinants, 77-5809
 - Comparative Immunodiffusion Test, 77-5809
- Virus, Feline Leukemia**
 - Antigens, Viral
 - Epidemiology, 77-5718
 - Carcinoma
 - RNA, Viral, 77-5715
 - Viral Proteins, 77-5715
 - Cell Membrane
 - Antigens, Viral, 77-5717
 - Lymphoma
 - Antibodies, Viral, 77-5892
 - RNA, Viral, 77-5715
 - Viral Proteins, 77-5715
 - Sarcoma
 - RNA, Viral, 77-5715
 - Viral Proteins, 77-5715
 - Viral Proteins
 - Antigenic Determinants, 77-5716
 - Isolation and Characterization, 77-5716
- Virus, Rauscher Murine Leukemia**
 - Antigenic Determinants, 77-5716
- Virus, Friend Murine Leukemia**
 - Antibodies, Viral
 - Cells, Cultured, 77-5732
 - Antigens, Heterogenetic
 - Virus Replication, 77-5888
 - Antigens, Viral
 - Cell Transformation, Neoplastic, 77-5767
 - Carcinogenic Activity
 - Immune Response, 77-5866
 - Cell Transformation, Neoplastic
 - Ultrastructural Study, 77-5767
 - Erythroleukemia
 - Isolation and Characterization, 77-5733
 - Glycoproteins
 - Cell Transformation, Neoplastic, 77-5767
 - Leukemia, Lymphocytic
 - Neoplasm Regression, Spontaneous, 77-5731
 - Lymphoma
 - Cells, Cultured, 77-5750
 - Immune Response, 77-5750
 - Macrophages
 - Immune Response, 77-5729
 - RNA, Messenger
 - DNA-RNA Hybridization, 77-5734
 - RNA, Viral
 - DNA-RNA Hybridization, 77-5734
- Virus, Friend Murine Leukemia (cont'd)**
 - Isolation and Characterization, 77-5733
- Virus, Helper**
 - Neoplasm Regression, Spontaneous, 77-5731
- Virus, Gazdar Murine Sarcoma**
 - Viral Proteins
 - Isolation and Characterization, 77-5751
 - Virus, Hamster Leukemia
 - DNA-RNA Hybridization, 77-5751
 - Virus, Moloney Murine Sarcoma
 - Antigenic Determinants, 77-5751
 - DNA-RNA Hybridization, 77-5751
- Virus, Gibbon Ape Leukemia**
 - Melanoma
 - Antibodies, Viral, 77-5810
- Virus, Gross Murine Leukemia**
 - Antigens, Viral
 - Cell Membrane, 77-5738
 - Carcinogenic Activity
 - Immune Response, 77-5866
 - Hodgkin's Disease
 - Antibodies, Viral, 77-5739
 - Leukemia
 - Antibodies, Viral, 77-5739
 - Leukemia, Lymphoblastic
 - Antibodies, Viral, 77-5739
 - Leukemia, Myeloblastic
 - Antibodies, Viral, 77-5739
 - Pregnancy
 - Antibodies, Viral, 77-5739
 - Virus, Radiation Leukemia
 - Antigenic Determinants, 77-5738
 - Antigens, Viral, 77-5738
 - DNA-RNA Hybridization, 77-5735
- Virus, Hamster C-Type RNA Tumor**
 - Benzo(a)pyrene
 - Cell Transformation, Neoplastic, 77-5773
- Virus, Hamster Leukemia**
 - Virus, Gazdar Murine Sarcoma
 - DNA-RNA Hybridization, 77-5751
- Virus, Hamster Sarcoma**
 - Cell Membrane
 - Cell Transformation, Neoplastic, 77-5774
 - Cell Transformation, Neoplastic
 - Peptides, 77-5774
- Virus, HEL-12**
 - Virus, C-Type RNA Tumor
 - Virus Replication, 77-5811
- Virus, Helper**
 - Leukemia, Lymphocytic
 - Neoplasm Regression, Spontaneous, 77-5731
 - Virus, Friend Murine Leukemia
 - Neoplasm Regression, Spontaneous, 77-5731
 - Virus, Radiation Leukemia
 - Virus, Murine Sarcoma, 77-5735
- Virus, Hepatitis**
 - Diethylamine, *N*-Nitroso-
 - Co-carcinogenic Activity, Monkey, 77-5608
 - Hepatoma
 - Diethylamine, *N*-Nitroso-, 77-5608
 - Ultrastructural Study, Monkey, 77-5608

- Virus, Herpes Saimiri**
 - Lymphoma
 - Marmoset, 77-5808
 - Virus, Epstein-Barr
 - Antigenic Determinants, 77-5809
 - Comparative Immunodiffusion Test, 77-5809
- Virus, Herpes Simplex**
 - Cell Transformation, Neoplastic
 - Histological Study, 77-5816
- Virus, Herpes Simplex 1**
 - DNA, Viral
 - Isolation and Characterization, 77-5817
 - Pathology
 - Epidemiology, 77-5422
 - Reverse Transcriptase
 - Cell Transformation, Neoplastic, 77-5812
 - RNA Polymerase
 - Cells, Cultured, 77-5813
 - Virus, C-Type RNA Tumor
 - Virus Replication, 77-5812
 - Virus, Herpes Simplex 2
 - DNA, Viral, 77-5817
- Virus, Herpes Simplex 2**
 - Antibodies, Viral
 - Epidemiology, 77-5422
 - Cells, Cultured
 - Thymidine Kinase, 77-5815
 - Cervix Neoplasms
 - Carcinoma, 77-5422
 - DNA Repair
 - Cells, Cultured, 77-5814
 - Estradiol, 77-5814
 - DNA, Viral
 - Isolation and Characterization, 77-5817
 - Thymidine Kinase, 77-5815
 - Reverse Transcriptase
 - Cell Transformation, Neoplastic, 77-5812
 - Viral Vaccines
 - Epidemiology, Review, 77-5423
 - Virus, C-Type RNA Tumor
 - Virus Replication, 77-5812
 - Virus, Herpes Simplex 1
 - DNA, Viral, 77-5817
- Virus, Kirsten Murine Sarcoma**
 - Cell Transformation, Neoplastic
 - Adenosine Cyclic 3',5' Monophosphate, 77-5748
 - Collagen, 77-5747
 - Liver, Rat, 77-5749
 - Epithelial Cells
 - Cell Transformation, Neoplastic, 77-5749
 - Fibrosarcoma
 - Cells, Cultured, 77-5749
 - Sarcoma
 - Cells, Cultured, 77-5749
- Virus, Leukemia**
 - Leukemia
 - Bone Marrow Cells, 77-5849
 - Isolation and Characterization, 77-5849
 - RNA, Viral
 - Isolation and Characterization, 77-5733
 - Virus, Simian Sarcoma
 - Antibody Specificity, 77-5849
- Virus-Like Particles**
 - Melanoma
- Virus-Like Particles (cont'd)**
 - Ultrastructural Study, 77-5853
 - Virus, Vesicular Stomatitis, 77-5853
 - Neoplasms, Vascular Tissue
 - Spleen, 77-5848
 - Ultrastructural Study, 77-5848
 - Prostatic Neoplasms
 - Adenocarcinoma, 77-5852
 - Ultrastructural Study, 77-5852
 - Uridine, 5-Bromo-2'-deoxy-
 - Liver, Rat, 77-5749
 - Virus, Abelson Murine Leukemia
 - Plasmacytoma, 77-5770
 - Virus, C-Type RNA Tumor
 - Antibodies, Viral, 77-5770
 - Virus, D-Type RNA Tumor
 - Isolation and Characterization, Squirrel Monkey 77-5781
 - Placenta, 77-5781
 - Virus, Papilloma
 - Ultrastructural Study, 77-5870
 - Virus, Rauscher Murine Leukemia
 - Mouse, 77-5727
- Virus, Marek's Disease Herpes**
 - Antigens, Neoplasm
 - Immunity, Cellular, 77-5880
 - Immunity, Cellular
 - Chicken, 77-5880
 - Lymphoma
 - Epidemiology, Review, 77-5424
 - Turkey
 - Histological Study, 77-5713
 - Viral Vaccines
 - Epidemiology, Review, 77-5424
- Virus, Mason-Pfizer Monkey**
 - Antigens, Viral
 - Antibodies, Neoplasm, 77-5891
 - Dexamethasone
 - Reverse Transcriptase, 77-5775
 - Virus Replication, 77-5775
 - Reverse Transcriptase
 - Antibody Specificity, 77-5777
 - Antigenic Determinants, 77-5777
 - Isolation and Characterization, 77-5777
 - RNA, Viral
 - DNA-RNA Hybridization, 77-5776, 77-5780
 - Uridine, 2'-Deoxy-5-iodo-
 - Reverse Transcriptase, 77-5775
 - Virus Replication, 77-5775
 - Virus, C-Type RNA Tumor
 - Virus Replication, 77-5775
 - Virus Replication
 - C-Type Particles, 77-5775
 - Ultrastructural Study, 77-5775
- Virus, Moloney Murine Leukemia**
 - Carcinogenic Activity
 - Immune Response, 77-5866
 - Cell Aggregation
 - Temperature Sensitive Mutants, 77-5742
 - Complement
 - Virus Replication, 77-5860
 - Immune Serums
 - Cell Transformation, Neoplastic, 77-5860
 - Virus Replication, 77-5860
 - Spleen
 - Immune Response, 77-5860

- Virus, Moloney Murine Leukemia (cont'd)**
 - Immunosuppression, 77-5860
- Virus, Moloney Murine Sarcoma**
 - Antigens, Viral, 77-5745
 - Immunity, Cellular, 77-5745
 - Immunosuppression, 77-5745
- Virus Replication**
 - Temperature Sensitive Mutants, 77-5742
 - Ultrastructural Study, 77-5742
- Virus, Moloney Murine Sarcoma**
 - Cell Transformation, Neoplastic
 - Collagen, 77-5747
 - DNA, Viral
 - Cell Transformation, Neoplastic, 77-5744
 - Lymphoma
 - Cells, Cultured, 77-5750
 - Immune Response, 77-5750
 - Neoplasms, Experimental
 - Adenosine Cyclic 3',5' Monophosphate, 77-5746
 - Guanosine Cyclic 3',5' Monophosphate, 77-5746
 - Prostaglandins E, 77-5746
 - Prostaglandins F, 77-5746
 - Sarcoma
 - Immune Response, 77-5874
- Virus, Gazdar Murine Sarcoma**
 - Antigenic Determinants, 77-5751
 - DNA-RNA Hybridization, 77-5751
- Virus, Moloney Murine Leukemia**
 - Antigens, Viral, 77-5745
 - Immunity, Cellular, 77-5745
 - Immunosuppression, 77-5745
- Virus, Moloney Murine Sarcoma-Leukemia**
 - Cell Transformation, Neoplastic
 - Temperature Sensitive Mutants, 77-5743
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Temperature Sensitive Mutants, 77-5743
 - Temperature Sensitive Mutants
 - Isolation and Characterization, 77-5743
 - Ultraviolet Rays
 - Temperature Sensitive Mutants, 77-5743
 - Virus Replication
 - Temperature Sensitive Mutants, 77-5743
- Virus, Murine Leukemia**
 - Actinomycin D
 - Reverse Transcriptase, 77-5741
 - Leukemia, Lymphocytic
 - Bone Marrow Cells, 77-5740
 - Immune Serums, 77-5740
 - Leukocytes, 77-5740
 - Oligonucleotides
 - Mice, AKR, 77-5768
 - Ribonuclease Resistance, 77-5768
 - Phosphoproteins
 - Isolation and Characterization, 77-5725
 - Reverse Transcriptase
 - Isolation and Characterization, 77-5741
 - RNA Polymerase
 - Cells, Cultured, 77-5763
 - RNA, Viral
 - Gel Electrophoresis, 77-5768
 - Mice, AKR, 77-5768
 - Oligonucleotides, 77-5768
 - Reverse Transcriptase, 77-5741
 - Viral Proteins
 - Isolation and Characterization, 77-5725
- Virus, Murine Mammary Tumor**
 - Antigenic Determinants
 - Strain Difference, 77-5757
 - Breast Neoplasms
 - Antigens, Viral, 77-5756
 - Estradiol
 - Antigens, Viral, 77-5753
 - Genetics
 - Epidemiology, 77-5429
 - Mammary Neoplasms, Experimental
 - Adenocarcinoma, 77-5755
 - Genetics, 77-5752
 - Strain Difference, 77-5755
 - Milk
 - Vertical Transmission, 77-5755
 - Spermatozoa
 - Vertical Transmission, 77-5755
 - 4,4'-Stilbenediol, α, α' -Diethyl-
 - Antigens, Viral, 77-5753
 - Viral Proteins
 - Antigenic Determinants, 77-5757
 - Virus Replication
 - Prolactin, 77-5754
- Virus, Murine Sarcoma**
 - Breast Neoplasms
 - Carcinoma, 77-5850
 - Cholanthrene, 3-Methyl-
 - Carcinogenic Activity, 77-5866
 - Immune Response, 77-5866
 - Virus, Radiation Leukemia
 - Virus, Helper, 77-5735
- Virus, Papilloma**
 - Antibodies, Viral
 - Immune Response, 77-5847
 - Antibody Formation
 - IgG, 77-5870
 - IgM, 77-5870
 - DNA, Viral
 - Isolation and Characterization, 77-5845, 77-5846
 - Virus-Like Particles
 - Ultrastructural Study, 77-5870
 - Warts
 - Isolation and Characterization, 77-5845, 77-5846
 - Ultrastructural Study, 77-5845
- Virus, Papova**
 - Antigens, Viral
 - Isolation and Characterization, 77-5807
 - Condylomata Acuminata
 - Case Report, 77-5844
- Virus, Papova BK**
 - Antigens, Viral
 - Isolation and Characterization, 77-5806, 77-5807
 - Ependymoma
 - Antigen-Antibody Reactions, 77-5843
 - Dosage Forms, 77-5843
 - Histological Study, Mouse, Hamster, 77-5843
 - Virus, SV40
 - Antigens, Viral, 77-5806
- Virus, Papova, JC**
 - Antigens, Viral
 - Isolation and Characterization, 77-5807
- Virus, Para-Adeno 12**
 - Neoplasms, Experimental
 - Histological Study, 77-5803

- Virus, Parvo**
 - Antigens, Viral
 - Temperature Sensitive Mutants, H-1 Virus, 77-5798
 - Ultrastructural Study, 77-5798
 - Cellular Inclusions
 - Antigens, Viral, 77-5798
 - Chromatin
 - Antigens, Viral, 77-5798
 - DNA Replication
 - Temperature Sensitive Mutants, H-1 Virus, 77-5798
 - Hemagglutinins, Viral
 - Temperature Sensitive Mutants, H-1 Virus, 77-5798
 - Virus Replication
 - Temperature Sensitive Mutants, H-1 Virus, 77-5798
 - Ultrastructural Study, 77-5798
 - Virus, SV40
 - Virus Replication, 77-5798
- Virus, Parvo H-1**
 - Virus Replication
 - Temperature Sensitive Mutants, 77-5797
 - Ultrastructural Study, 77-5797
- Virus, Polyoma**
 - Antibodies, Viral
 - Mouse, 77-5759
 - Pregnancy, Animal, 77-5759
 - Cell Transformation, Neoplastic
 - Cell-Cycle Kinetics, 77-5698
 - Histological Study, 77-5698
 - DNA Polymerase
 - Enzymatic Activity, 77-5758
 - DNA, Viral
 - Cell Transformation, Neoplastic, 77-5760
 - Isolation and Characterization, 77-5761
 - Temperature Sensitive Mutants, 77-5760
 - Viral Proteins
 - Isolation and Characterization, 77-5762
 - Temperature Sensitive Mutants, 77-5762
 - Virus Replication
 - Isolation and Characterization, 77-5761
- Virus, Polyoma, BK**
 - Antigens, Viral
 - Urine, 77-5842
- Virus, Polyoma, JC**
 - Antigens, Viral
 - Urine, 77-5842
- Virus, Precerutti-Law Leukemia**
 - Immune Response
 - Mouse, 77-5864
- Virus, Radiation Leukemia**
 - Antigenic Determinants
 - Antigens, Viral, 77-5738
 - Antigens, Viral
 - Cell Membrane, 77-5738
 - Macrophages, 77-5871
 - Histocompatibility Antigens
 - Genetics, 77-5736, 77-5737
 - T-Lymphocytes
 - Immunity, Cellular, 77-5871
 - Macrophages
 - Immunity, Cellular, 77-5871
 - T-Lymphocytes, 77-5871
 - Virus, Gross Murine Leukemia
 - Antigenic Determinants, 77-5738
 - Antigens, Viral, 77-5738
- Virus, Radiation Leukemia (cont'd)**
 - DNA-RNA Hybridization, 77-5735
 - Virus, Murine Sarcoma
 - Virus, Helper, 77-5735
 - Virus, Rauscher Murine Leukemia
 - DNA-RNA Hybridization, 77-5735
- Virus, Rauscher Murine Leukemia**
 - Antibodies, Viral
 - Reverse Transcriptase, 77-5741
 - Carcinogenic Activity
 - Immune Response, 77-5866
 - Hycanthone
 - Cell Transformation, Neoplastic, 77-5534
 - Leukemia
 - Mouse, 77-5857
 - Lucanthone
 - Cell Transformation, Neoplastic, 77-5534
 - Phosphoproteins
 - Isolation and Characterization, 77-5725
 - Viral Proteins
 - Isolation and Characterization, 77-5725, 77-5726
 - 77-5728, 77-5772
 - Virus, Feline Leukemia
 - Antigenic Determinants, 77-5716
 - Virus-Like Particles, C-Type
 - Mouse, 77-5727
 - Virus, Radiation Leukemia
 - DNA-RNA Hybridization, 77-5735
 - Virus Replication
 - Cells, Cultured, 77-5726
- Virus, RD-114**
 - Carcinoma
 - RNA, Viral, 77-5715
 - Viral Proteins, 77-5715
 - Lymphoma
 - RNA, Viral, 77-5715
 - Viral Proteins, 77-5715
 - Sarcoma
 - RNA, Viral, 77-5715
 - Viral Proteins, 77-5715
 - Viral Proteins
 - Isolation and Characterization, 77-5772
- Virus Replication**
 - Burkitt's Lymphoma
 - Virus, Adeno 5, 77-5827
 - Leukemia
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-5765
 - Lymphoma
 - Marmoset, 77-5808
 - Neoplasms, Radiation-Induced
 - Virus, C-Type RNA Tumor, 77-5764
 - Prolactin
 - Cells, Cultured, 77-5754
 - Somatotropin
 - Cells, Cultured, 77-5754
 - Virus, Adeno 5
 - DNA, Viral, 77-5836
 - Virus, Adeno 2 - SV40 Hybrid
 - Viral Proteins, 77-5805
 - Virus, Avian Reticuloendotheliosis
 - Isolation and Characterization, 77-5701
 - Virus, Avian Sarcoma
 - Isolation and Characterization, 77-5701
 - Virus, Bovine Leukemia
 - Fetus, 77-5722
 - Ultrastructural Study, 77-5720

Virus Replication (cont'd)

- Virus, C-Type RNA Tumor
 - Virus, HEL-12, 77-5811
- Virus, Epstein Barr
 - Virus, Adeno 5, 77-5827
- Virus, Friend Murine Leukemia
 - Antigens, Heterogenetic, 77-5888
- Virus, Herpes Simplex 1
 - Virus, C-Type RNA Tumor, 77-5812
- Virus, Herpes Simplex 2
 - Virus, C-Type RNA Tumor, 77-5812
- Virus, Mason-Pfizer Monkey
 - C-Type Particles, 77-5775
 - Dexamethasone, 77-5775
 - Ultrastructural Study, 77-5775
 - Uridine, 2'-Deoxy-5-iodo-, 77-5775
 - Virus, C-Type RNA Tumor, 77-5775
- Virus, Moloney Murine Leukemia
 - Complement, 77-5860
 - Immune Serums, 77-5860
 - Temperature Sensitive Mutants, 77-5742
 - Ultrastructural Study, 77-5742
- Virus, Moloney Murine Sarcoma-Leukemia
 - Temperature Sensitive Mutants, 77-5743
- Virus, Murine Mammary Tumor
 - Prolactin, 77-5754
- Virus, Parvo
 - Temperature Sensitive Mutants, H-1 Virus, 77-5798
 - Ultrastructural Study, 77-5798
- Virus, Parvo H-1
 - Temperature Sensitive Mutants, 77-5797
 - Ultrastructural Study, 77-5797
- Virus, Polyoma
 - Isolation and Characterization, 77-5761
- Virus, Rauscher Murine Leukemia
 - Cells, Cultured, 77-5726
- Virus, Simian Sarcoma-Associated
 - Cells, Cultured, 77-5778
- Virus, SV40
 - Antigens, Viral, 77-5785
 - DNA, Viral, 77-5800
 - Isolation and Characterization, 77-5787
 - Viral Proteins, 77-5789
 - Virus, Parvo, 77-5798

Virus, RNA Tumor

- Eels
 - Carcinogenic Potential, Review, 77-5426
- Papilloma
 - Epidemiology, Eels, Review, 77-5426
- Reverse Transcriptase
 - DNA, Viral, 77-5709

Virus, Rous-Associated

- Cell Membrane
 - Binding, 77-5707
- RNA, Viral
 - Cells, Cultured, 77-5705

Virus, Rous Sarcoma

- Antigens, Viral
 - Cell Transformation, Neoplastic, 77-5708, 77-5711
- Cell Membrane
 - Cells, Cultured, 77-5706
- Cell Transformation, Neoplastic
 - Adenosine Deaminase, 77-5702
 - Cell Cycle-Kinetics, 77-5698
 - Histological Study, 77-5698, 77-5708
- DNA Repair

Virus, Rous Sarcoma (cont'd)

- DNA Replication, 77-5703
- DNA-RNA Hybridization, 77-5703
- Lipids
 - Cell Membrane, 77-5706
- Neoplasms, Experimental
 - Immune Response, Chicken, 77-5865
- Quinoline, 4-Nitro-, 1-Oxide
 - DNA Repair, 77-5703
- Reverse Transcriptase
 - RNA Replication, 77-5700
- Ribonuclease
 - RNA Replication, 77-5700
- RNA, Viral
 - Cells, Cultured, 77-5705
 - DNA-RNA Hybridization, 77-5700
 - Isolation and Characterization, 77-5705
- Sarcoma
 - Cell Transformation, Neoplastic, 77-5704
 - Glucosaminidase, 77-5573
 - Lysosomes, 77-5573
- Ultraviolet Rays
 - DNA Repair, 77-5703
- Virus, Avian Myeloblastosis
 - Reverse Transcriptase, 77-5700
 - Ribonuclease, 77-5700

Virus, Sendai

- Antigens, Viral
 - Cells, Cultured, 77-5820

Virus, Simian Sarcoma

- Antigens, Viral
 - Antibodies, Neoplasm, 77-5891
- Melanoma
 - Antibodies, Viral, 77-5810
- Viral Proteins
 - Isolation and Characterization, 77-5779
- Virus, Leukemia
 - Antibody Specificity, 77-5849

Virus, Simian Sarcoma-Associated

- Reverse Transcriptase
 - Enzymatic Activity, 77-5778
- Viral Proteins
 - Isolation and Characterization, 77-5778
- Virus Replication
 - Cells, Cultured, 77-5778

Virus, Spleen Focus-Forming

- RNA, Viral
 - Isolation and Characterization, 77-5733

Virus, Spleen Necrosis

- see* Virus, Avian Reticuloendotheliosis

Virus, SV40

- Antigens, Neoplasm
 - Hamster, 77-5794
- Antigens, Viral
 - Binding, 77-5801
 - Chromatin, 77-5801
 - DNA, 77-5801
 - HeLa Cells, 77-5802
 - Isolation and Characterization, 77-5807
 - Mouse, 77-5884
 - Virus, Papova, BK, 77-5806
- Cell Adhesion
 - Cell Transformation, Neoplastic, 77-5972
- Cell Transformation, Neoplastic

Virus, SV40 (cont'd)

- Cell-Cycle Kinetics, 77-5968
- Insulin, 77-5788
- Isolation and Characterization, 77-5792
- Karyotyping, 77-5783
- Cells, Cultured
 - Mutagenic Activity, 77-5796
- Cellulose, Methyl Ether
 - Clone Cells, 77-5783
- Chromosome Aberrations
 - Review, 77-5435
- Clone Cells
 - Agglutination, 77-5783
 - Cell Transformation, Neoplastic, 77-5783
 - Concanavalin A, 77-5783
 - DNA, 77-5783
- Cytochalasin B
 - Cell Division, 77-5973
- DNA Replication
 - DNA, Viral, 77-5791
 - Temperature Sensitive Mutants, 77-5795
- DNA-RNA Hybridization
 - Ultrastructural Study, 77-5786
- DNA, Viral
 - Antigenic Determinants, 77-5790
 - DNA-RNA Hybridization, 77-5786
 - Isolation and Characterization, 77-5790, 77-5799
 - Ultrastructural Study, 77-5799, 77-5800
- Glutamine
 - Mutagenic Activity, 77-5622
 - Temperature Sensitive Mutants, 77-5622
- Growth Substances
 - Cell-Cycle Kinetics, 77-5968
 - Phosphoinositides, 77-5968
- Histocompatibility Antigens
 - Detergents, 77-5885
 - Isolation and Characterization, 77-5885
- Histones
 - DNA, Viral, 77-5789
- Neoplasms, Experimental
 - Histological Study, 77-5803
- Phosphoinositides
 - Cell Transformation, Neoplastic, 77-5968
- Plasminogen
 - Cell-Cycle Kinetics, 77-5784
 - Cells, Cultured, 77-5784
- RNA, Messenger
 - Antigenic Determinants, 77-5790
 - Isolation and Characterization, 77-5787
- RNA, Viral
 - DNA-RNA Hybridization, 77-5786
- Sarcoma
 - Histocompatibility Antigens, 77-5885
- Teratoid Tumor
 - Cells, Cultured, 77-5793
- Ultraviolet Rays
 - DNA Replication, 77-5795
 - Mutagenic Activity, 77-5795
- Viral Proteins
 - DNA, Viral, 77-5789
 - Virus Replication, 77-5789
- Virus, Adeno 2 - SV40 Hybrid
 - DNA Repair, 77-5805
- Virus, Parvo
 - Virus Replication, 77-5798
- Virus Replication
 - Antigens, Viral, 77-5785

Virus, SV40 (cont'd)

- DNA, Viral, 77-5800
- Isolation and Characterization, 77-5787
- Virus, Vesicular Stomatitis**
 - Melanoma
 - Alanine, 3-(3,4-Dihydroxyphenyl)-, 77-5853
 - Ultrastructural Study, 77-5853
 - Uridine, 2'-Deoxy-5-iodo-, 77-5853
 - Virus-Like Particles, 77-5853
- Vitamin C**
 - see Ascorbic Acid
- Warts**
 - Virus, Papilloma
 - Isolation and Characterization, 77-5845, 77-5846
 - Ultrastructural Study, 77-5845
- Water**
 - Acetohydroxamic Acid, *N*-Fluoren-2-yl-Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-, 77-5470
- Water Pollutants**
 - Ethylene, Tetrachloro-Carcinogenic Potential, 77-5408
 - Hydatidiform Mole, 77-5598
- Water Pollutants, Chemical**
 - Lung Neoplasms
 - Adenoma, 77-5493
- Water Pollution**
 - Arsenic
 - Epidemiology, 77-5637
 - Epidemiology, Taiwan, 77-5638
 - Asbestos
 - Lung Neoplasms, 77-5957
 - Pancreatic Neoplasms, 77-5957
 - Stomach Neoplasms, 77-5957
 - Carcinogen, Chemical
 - Concentration Levels, Review, 77-5402
 - Fish
 - Epidemiology, Review, 77-5407
 - Neoplasms
 - Epidemiology, 77-5956
 - Fish, 77-5958
 - Organic Compounds
 - Isolation and Characterization, Review, 77-5403
 - Papilloma
 - Epidemiology, Eels, Review, 77-5426
 - Plutonium
 - Food Chain, 77-5658
 - Plutonium Radioisotopes
 - Food Chain, 77-5658
 - Salmonella typhimurium*
 - Mutagenic Activity, 77-5494
 - Skin Neoplasms
 - Arsenic, 77-5638
 - Fish, 77-5407
- Xanthine, 3-Isobutyl-1-methyl-**
 - Hepatoma
 - Butyric Acid, 2-Amino-4-(ethylthio)-, 77-5499
- Xeroderma Pigmentosum**
 - Chromosome Aberrations
 - Review, 77-5438
 - Skin Neoplasms
 - Carcinoma, Basal Cell, 77-5434
 - Carcinoma, Epidermoid, 77-5434
 - Melanoma, 77-5434
 - Ultraviolet Rays
 - DNA Repair, 77-5433, 77-5434

Chemical Abstracts Service Registry Number Index

- 50-02-2, 77-5775, 77-5987
50-07-7, 77-5627, 77-5629
50-18-0, 77-5401, 77-5533
50-21-5, 77-5618
50-22-6, 77-5995
50-23-7, 77-5528, 77-5995
50-24-8, 77-5782
50-27-1, 77-5520
50-28-2, 77-5519, 77-5577, 77-5753
77-5814, 77-5995, 77-5996
50-29-3, 77-5485, 77-5492, 77-5495
77-5958
50-32-8, 77-5544, 77-5545, 77-5549
77-5550, 77-5551, 77-5552
77-5553, 77-5554, 77-5555
77-5556, 77-5557, 77-5558
77-5559, 77-5560, 77-5562
77-5564, 77-5565, 77-5566
77-5567, 77-5568, 77-5569
77-5570, 77-5596, 77-5627
77-5630, 77-5631, 77-5673
77-5773, 77-5868, 77-5968
50-33-9, 77-5451
50-44-2, 77-5535
50-50-0, 77-5520
50-53-3, 77-5602
50-76-0, 77-5546, 77-5628, 77-5741
50-78-2, 77-5451
50-81-7, 77-5599, 77-5983
50-91-9, 77-5758
51-03-6, 77-5602
51-48-9, 77-5686
51-79-6, 77-5497, 77-5498
51-83-2, 77-5499
52-24-4, 77-5629
52-39-1, 77-5995
52-68-6, 77-5500
52-90-4, 77-5505
53-16-7, 77-5413
53-70-3, 77-5544, 77-5546, 77-5547
77-5548
53-86-1, 77-5451
53-95-2, 77-5415, 77-5465, 77-5466
77-5470, 77-5471, 77-5472
53-96-3, 77-5415, 77-5427, 77-5449
77-5466, 77-5467, 77-5469
77-5471, 77-5472, 77-5473
77-5920, 77-5922
54-42-2, 77-5775, 77-5853
55-18-5, 77-5401, 77-5427, 77-5603
77-5604, 77-5608, 77-5627
77-5919, 77-5920
55-80-1, 77-5480, 77-5481
56-23-5, 77-5546, 77-5547, 77-5958
56-29-1, 77-5569
56-49-5, 77-5449, 77-5539, 77-5544
77-5546, 77-5547, 77-5548
77-5554, 77-5566, 77-5583
77-5584, 77-5585, 77-5586
77-5587, 77-5588, 77-5592
77-5631, 77-5766, 77-5854
77-5855, 77-5863, 77-5866
77-5869, 77-5886, 77-5909
56-53-1, 77-5445, 77-5517, 77-5518
77-5519, 77-5520, 77-5753
56-55-3, 77-5545, 77-5549, 77-5567
77-5596
56-57-5, 77-5583, 77-5623, 77-5624
77-5625, 77-5629, 77-5631
77-5703
56-85-9, 77-5622
57-13-6, 77-5978
57-14-7, 77-5502
57-63-6, 77-5520, 77-5525, 77-5526
57-83-0, 77-5524, 77-5995
57-97-6, 77-5544, 77-5545, 77-5548
77-5570, 77-5571, 77-5572
77-5573, 77-5574, 77-5575
77-5576, 77-5577, 77-5578
77-5579, 77-5630, 77-5765
77-5996
58-08-2, 77-5479, 77-5629, 77-5631
77-5679
58-22-0, 77-5996
58-25-3, 77-5602
58-27-5, 77-5625
59-14-3, 77-5632
59-30-3, 77-5466
59-87-0, 77-5625
59-89-2, 77-5604
59-92-7, 77-5853
60-11-7, 77-5427, 77-5482
60-18-4, 77-5986
60-80-0, 77-5569
60-92-4, 77-5746, 77-5748
62-49-7, 77-5706
62-50-0, 77-5627, 77-5629, 77-5632
77-5680
62-53-3, 77-5478, 77-5479
62-73-7, 77-5509
62-75-9, 77-5482, 77-5599, 77-5603
77-5604, 77-5609, 77-5610
77-5611, 77-5627, 77-5681
63-25-2, 77-5600
64-17-5, 77-5451, 77-5782, 77-5943
66-27-3, 77-5401, 77-5626, 77-5627
77-5629, 77-5990
66-81-9, 77-5986
67-21-0, 77-5499
67-66-3, 77-5958
67-73-2, 77-5540
68-22-4, 77-5523
68-23-5, 77-5523
68-26-8, 77-5492
70-18-8, 77-5466, 77-5505
70-25-7, 77-5536, 77-5537, 77-5580
77-5620, 77-5622, 77-5623
77-5630, 77-5631, 77-5680
77-5681, 77-5743
71-43-2, 77-5551, 77-5552
71-44-3, 77-5976
72-33-3, 77-5521, 77-5525, 77-5527
72-54-8, 77-5485
72-55-9, 77-5485
72-63-9, 77-5921
74-79-3, 77-5602, 77-5821
74-82-8, 77-5476
75-01-4, 77-5401, 77-5417, 77-5495
77-5496, 77-5944, 77-5945
75-21-8, 77-5489
75-25-2, 77-5493
75-60-5, 77-5641
76-44-8, 77-5490
77-78-1, 77-5629
79-01-6, 77-5488, 77-5495
79-06-1, 77-5495

82-92-8, 77-5602
85-01-8, 77-5545, 77-5596
86-74-8, 77-5567
87-65-0, 77-5484
90-15-3, 77-5541
91-20-3, 77-5541
91-64-5, 77-5569
91-80-5, 77-5602
92-04-6, 77-5484
92-52-4, 77-5485
92-87-5, 77-5478
92-93-3, 77-5473
94-59-7, 77-5516
95-53-4, 77-5479
96-09-3, 77-5542
96-20-8, 77-5706
97-56-3, 77-5482
99-56-9, 77-5435
100-42-5, 77-5495
100-46-9, 77-5609
100-63-0, 77-5964
100-75-4, 77-5603, 77-5604
100-97-0, 77-5602
101-42-8, 77-5602
103-85-5, 77-5986
104-46-1, 77-5516
106-88-7, 77-5488
106-89-8, 77-5488
107-20-0, 77-5411
108-01-0, 77-5706
108-05-4, 77-5597
109-76-2, 77-5991
109-83-1, 77-5706
110-60-1, 77-5976
110-89-4, 77-5602
112-18-5, 77-5602
118-74-1, 77-5483
120-58-1, 77-5516
121-79-9, 77-5610
122-03-2, 77-5516
124-20-9, 77-5976
124-40-3, 77-5610
124-58-3, 77-5641
126-99-8, 77-5597

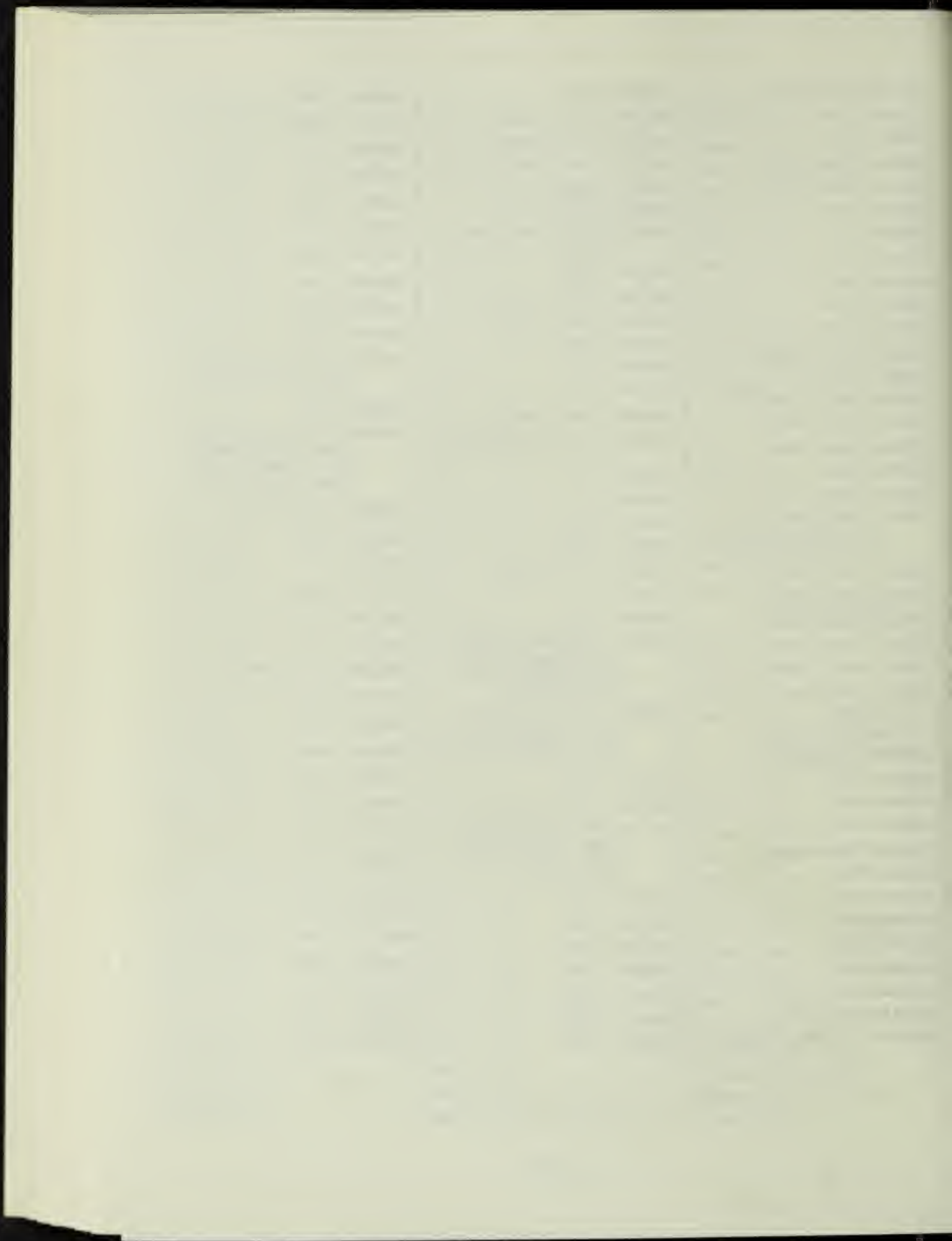
127-07-1, 77-5758
127-18-4, 77-5408, 77-5495
127-47-9, 77-5620
128-37-0, 77-5610
129-00-0, 77-5549, 77-5550, 77-5567
77-5596, 77-5631
130-15-4, 77-5541
134-03-2, 77-5610
135-19-3, 77-5541
140-67-0, 77-5516
140-79-4, 77-5603
141-43-5, 77-5706
147-94-4, 77-5758
149-29-1, 77-5514
151-18-8, 77-5983
154-17-6, 77-5618
192-97-2, 77-5596
205-82-3, 77-5596
205-99-2, 77-5596
206-44-0, 77-5567, 77-5596
207-08-9, 77-5596
215-58-7, 77-5544
217-59-4, 77-5596
218-01-9, 77-5567, 77-5596
297-76-7, 77-5523
298-81-7, 77-5668, 77-5669, 77-5670
77-5671, 77-5672
302-01-2, 77-5504
302-79-4, 77-5620
303-47-9, 77-5515
306-37-6, 77-5501
315-22-0, 77-5505
320-67-2, 77-5532
359-48-8, 77-5491
363-24-6, 77-5746
363-49-5, 77-5465
427-51-0, 77-5523
446-86-6, 77-5579
471-29-4, 77-5602
479-50-5, 77-5534, 77-5602
511-09-1, 77-5577
521-12-0, 77-5577
524-42-5, 77-5541
540-49-8, 77-5487
540-73-8, 77-5500, 77-5503, 77-5504

551-11-1, 77-5746
585-08-0, 77-5543
590-96-5, 77-5537
592-62-1, 77-5475, 77-5536
595-33-5, 77-5523
604-59-1, 77-5548
607-30-7, 77-5472
607-57-8, 77-5473
613-13-8, 77-5596
613-47-8, 77-5472
684-93-5, 77-5616, 77-5617, 77-5619
745-65-3, 77-5746
759-73-9, 77-5612, 77-5613, 77-5614
77-5615
869-01-2, 77-5617
924-16-3, 77-5604
930-55-2, 77-5603
962-32-3, 77-5543, 77-5545
979-32-8, 77-5520
1024-57-3, 77-5490
1147-55-3, 77-5466
1162-65-8, 77-5406, 77-5506, 77-5507
77-5508, 77-5509, 77-5510
77-5511, 77-5512, 77-5513
1314-20-1, 77-5945
1327-52-2, 77-5641
1327-53-3, 77-5636, 77-5641
1332-21-4, 77-5410, 77-5417, 77-5644
77-5645, 77-5646, 77-5647
77-5952, 77-5953, 77-5954
77-5955, 77-5957
1385-95-1, 77-5511
1403-17-4, 77-5474
1421-85-8, 77-5543
1694-09-3, 77-5477
1948-33-0, 77-5610
2278-22-0, 77-5418
2345-28-0, 77-5974
2541-69-7, 77-5580
2740-52-5, 77-5527
3105-97-3, 77-5534
3124-93-4, 77-5521, 77-5527
3137-73-3, 77-5521
3416-21-5, 77-5543, 77-5584
3688-53-7, 77-5462, 77-5463
3771-19-5, 77-5531

3817-11-6, 77-5606, 77-5978
 4176-88-9, 77-5620
 5697-56-3, 77-5452
 6051-87-2, 77-5548
 6098-44-8, 77-5468, 77-5470
 6530-27-4, 77-5472
 6795-23-9, 77-5513
 6807-96-1, 77-5510
 6810-26-0, 77-5472
 6898-94-8, 77-5649
 6949-28-6, 77-5604
 7439-92-1, 77-5412, 77-5634, 77-5873
 7439-96-5, 77-5634
 7440-02-0, 77-5412, 77-5634, 77-5635
 7440-07-5, 77-5659, 77-5662
 7440-08-6, 77-5656, 77-5657
 7440-22-4, 77-5634
 7440-24-6, 77-5665
 7440-38-2, 77-5412, 77-5637, 77-5638
 77-5639, 77-5640, 77-5641
 77-5945, 77-5947
 7440-41-7, 77-5412, 77-5634
 7440-43-9, 77-5412, 77-5634
 7440-47-3, 77-5412, 77-5634
 7440-48-4, 77-5412, 77-5634
 7631-89-2, 77-5642, 77-5643
 7632-00-0, 77-5599, 77-5600, 77-5602
 77-5610
 7647-17-8, 77-5666
 7665-99-8, 77-5499, 77-5746
 7697-37-2, 77-4659
 7782-39-0, 77-5567
 7782-49-2, 77-5480
 7782-77-6, 77-5601, 77-5604
 7791-14-2, 77-5491
 8001-28-3, 77-5624
 8002-43-5, 77-5481
 8007-70-3, 77-5516
 8016-88-4, 77-5516
 8049-97-6, 77-5986
 8063-94-3, 77-5417, 77-5946
 9001-45-0, 77-5472, 77-5563, 77-5594

9001-60-9, 77-5656
 9001-66-5, 77-5609, 77-5642
 9001-77-8, 77-5594, 77-5656
 9001-78-9, 77-5656, 77-5994
 9001-91-6, 77-5784
 9002-60-2, 77-5528
 9002-62-4, 77-5578, 77-5754, 77-5995
 77-5996
 9002-71-5, 77-5686
 9002-72-6, 77-5754
 9002-86-2, 77-5417, 77-5946
 9004-10-8, 77-5788
 9004-67-5, 77-5783
 9008-11-1, 77-5684
 9012-42-4, 77-5992, 77-5997
 9035-50-1, 77-5491, 77-5492, 77-5553
 77-5555
 10043-92-2, 77-5419
 10048-13-2, 77-5510
 10098-97-2, 77-5665
 10588-01-9, 77-5597
 11028-71-0, 77-5588, 77-5783
 11041-12-6, 77-5474
 11097-69-1, 77-5506
 12001-28-4, 77-5410, 77-5417, 77-5644
 77-5645, 77-5646, 77-5647
 77-5952, 77-5953, 77-5954
 77-5955, 77-5957
 12001-29-5, 77-5410, 77-5417, 77-5644
 77-5645, 77-5646, 77-5647
 77-5952, 77-5953, 77-5954
 77-5955, 77-5957
 12035-72-2, 77-5412
 12059-95-9, 77-5660, 77-5661
 12172-73-5, 77-5410, 77-5417, 77-5644
 77-5645, 77-5646, 77-5647
 77-5952, 77-5953, 77-5954
 77-5955, 77-5957
 12587-46-1, 77-5697
 13020-80-9, 77-5452
 13256-06-9, 77-5604
 13345-25-0, 77-5561
 13394-86-0, 77-5473
 13463-39-3, 77-5635
 13966-05-7, 77-5665

13967-73-2, 77-5665
 13981-52-7, 77-5658
 14016-29-6, 77-5510
 14119-33-6, 77-5658
 14158-27-1, 77-5665
 14930-96-2, 77-5973
 15117-48-3, 77-5658
 15663-27-1, 77-5681
 16301-26-1, 77-5473
 16338-97-9, 77-5605
 16561-29-8, 77-5536, 77-5537, 77-5538
 77-5539, 77-5540, 77-5561
 16812-54-7, 77-5412
 17068-78-9, 77-5410, 77-5417, 77-5644
 77-5645, 77-5646, 77-5647
 77-5952, 77-5953, 77-5954
 77-5955, 77-5957
 17070-44-9, 77-5680, 77-5681
 17924-92-4, 77-5414
 20535-83-5, 77-5503
 23107-12-2, 77-5505
 24554-26-5, 77-5464
 24928-17-4, 77-5539
 24961-39-5, 77-5479, 77-5581
 25013-16-5, 77-5610
 25614-03-3, 77-5530
 25843-45-2, 77-5474
 29129-66-6, 77-5522
 31005-02-4, 77-5569
 32450-56-9, 77-5620
 36504-66-2, 77-5543
 37574-47-3, 77-5542, 77-5543
 38252-74-3, 77-5978
 53459-39-5, 77-5484
 53905-37-6, 77-5484
 56892-30-9, 77-5560
 57303-99-8, 77-5561
 59080-40-9, 77-5486



Wiswesser Line Notation Index

AG, 77-5634
 AS, 77-5412, 77-5637, 77-5638, 77-5639, 77-5640, 77-5641
 77-5945, 77-5947
 AS2.O3, 77-5636, 77-5641
 BE, 77-5412, 77-5634
 CD, 77-5412, 77-5634
 CO, 77-5412, 77-5634
 CR, 77-5412, 77-5634
 MN, 77-5634
 NA..AS-O-Q3, 77-5642, 77-5643
 NA..N-O-Q, 77-5599, 77-5600, 77-5602, 77-5610
 NI, 77-5412, 77-5634, 77-5635
 NI3.S2, 77-5412
 PB, 77-5412, 77-5634, 77-5873
 PO, 77-5656, 77-5657, 77-5658
 PU, 77-5658, 77-5659, 77-5662
 PU..O2, 77-5660, 77-5661
 RN, 77-5419
 SE, 77-5480
 SR, 77-5665
 TH..O2, 77-5945
 CR O2 G2, 77-5491
 CS G, 77-5666
 EYEE, 77-5493
 EU1E, 77-5487
 G 6-R, 77-5483
 GR BQ DR DG, 77-5484
 GR BQ DR DG CQ, 77-5484
 GXGG YR DG&R DG, 77-5485, 77-5492, 77-5495, 77-5958
 GXGGG, 77-5546, 77-5547, 77-5958
 GXGGYQPO&O1&O1, 77-5500
 GYGG, 77-5958
 GYGUYGG, 77-5408, 77-5495
 GYGUYR DG&R DG, 77-5485
 GYGU1G, 77-5488, 77-5495
 GYGU1OPO&O1&O1, 77-5509
 GYGYR DG&R DG, 77-5485
 GIU1, 77-5401, 77-5417, 77-5495, 77-5496, 77-5944, 77-5945
 L B656 HHJ EMV1, 77-5415, 77-5427, 77-5449, 77-5466
 77-5467, 77-5469, 77-5471, 77-5472, 77-5473
 77-5920, 77-5922
 L B656 HHJ ENQV1, 77-5415, 77-5465, 77-5466, 77-5470
 77-5471, 77-5472

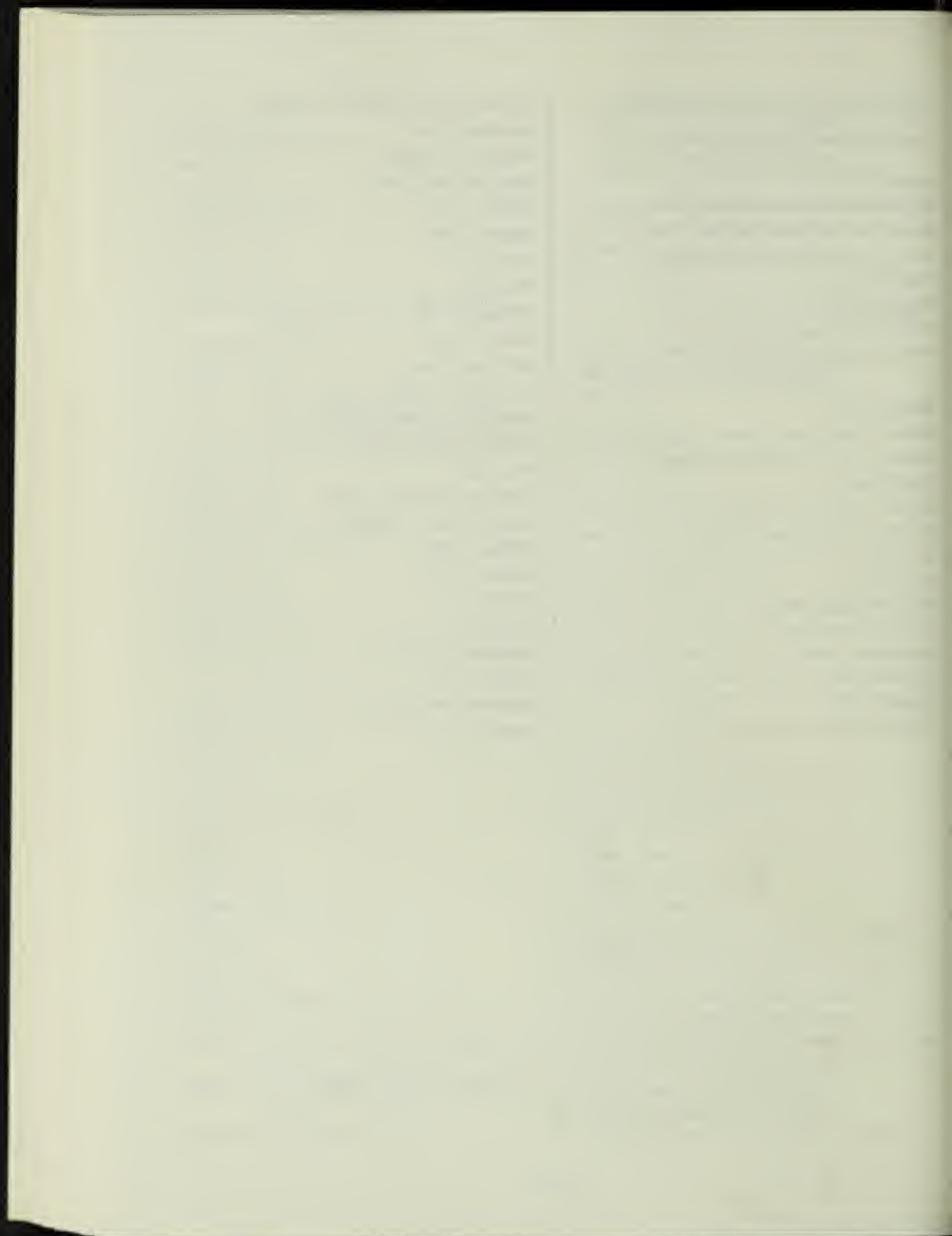
L B656 HHJ ENW, 77-5473
 L B666J, 77-5545, 77-5596
 L C555 A DU IUTJ AG AG BG FG HG IG JG, 77-5490
 L C65 K666 1A TJ, 77-5596
 L C6566 1A PJ, 77-5567, 77-5596
 L C666J EZ, 77-5596
 L D6 B666J, 77-5545, 77-5549, 77-5567, 77-5596
 L D6 B666J C J, 77-5544, 77-5545, 77-5548, 77-5570
 77-5571, 77-5572, 77-5573, 77-5574, 77-5575
 77-5576, 77-5577, 77-5578, 77-5579, 77-5630
 77-5765, 77-5996
 L D6 B666J J, 77-5580
 L D6 B666J J1E, 77-5479, 77-5581
 L D6 B6666 2AB TJ, 77-5544, 77-5545, 77-5549, 77-5550
 77-5551, 77-5552, 77-5553, 77-5554, 77-5555
 77-5556, 77-5557, 77-5558, 77-5559, 77-5560
 77-5562, 77-5564, 77-5565, 77-5566, 77-5567
 77-5568, 77-5569, 77-5570, 77-5596, 77-5627
 77-5630, 77-5631, 77-5673, 77-5773, 77-5868
 77-5968
 L D6 B6666 2AB TJ GQ HQ, 77-5561
 L D6 B6666 2AB TJ PQ, 77-5560
 L D6 C6566 1A TJ, 77-5596
 L D6 J6 C666J, 77-5544
 L D6666 B6 2AB TJ, 77-5596
 L E5 B666 FVTTT&J E OQ, 77-5413
 L E5 B666 OV MUTJ A CQ E FV1Q FQ -B&ACEF
 77-5528, 77-5995
 L E5 B666 OV MUTJ A E FQ -B&AEF, 77-5996
 L E5 B666 OV MUTJ A E FV1 -B&AEF, 77-5524, 77-5995
 L E5 B666TTT&J E FQ F1UU1 OQ, 77-5520, 77-5525
 77-5526
 L E5 B666TTT&J E FQ GQ OQ, 77-5520
 L E5 B666TTT&J E FQ OQ, 77-5519, 77-5577, 77-5753
 77-5814, 77-5995, 77-5996
 L E6 B666J, 77-5567, 77-5596
 L E6 D6656 1A T&&&T&J R, 77-5449, 77-5539, 77-5544
 77-5546, 77-5547, 77-5548, 77-5554, 77-5566
 77-5583, 77-5584, 77-5585, 77-5586, 77-5587
 77-5588, 77-5592, 77-5631, 77-5766, 77-5854
 77-5855, 77-5863, 77-5866, 77-5869, 77-5886
 77-5909
 L G6 D6 B666J, 77-5544, 77-5546, 77-5547, 77-5548
 L6UTJ A A B1U1Y&UZU1YU1VQ C -T, 77-5620
 L6UTJ A BL/U1Y&U2/ 2Q C C -T, 77-5492
 L64TJ A B1U1Y&U2U1Y&U2OV1 C C, 77-5620
 L66 BV EVJ, 77-5541
 L66 BV EVJ C, 77-5625

L66 BVVJ, 77-5541
 L66&TJ GR DOXVQ, 77-5531
 L66J, 77-5541
 L66J BMQ, 77-5472
 L66J BOVM1, 77-5600
 L66J BQ, 77-5541
 L66J CMQ, 77-5472
 L66J CQ, 77-5541
 L666 B6 2AB PJ, 77-5549, 77-5550, 77-5567, 77-5596
 77-5631
 NA2 CR2-05-Q2, 77-5597
 OC 4-NI-, 77-5635
 ONN1&1, 77-5482, 77-5599, 77-5603, 77-5604, 77-5609
 77-5610, 77-5611, 77-5627, 77-5681
 ONN2&2, 77-5401, 77-5427, 77-5603, 77-5604, 77-5608
 77-5627, 77-5919, 77-5920
 ONN4&4, 77-5604
 ONN5&5, 77-5604
 ON1&U&1, 77-5474
 ON1&UN1OV1, 77-5475, 77-5536
 Q-AS-QO&1, 77-5641
 QMR DR, 77-5472
 QR BQ CQ EVO3, 77-5610
 QR DQ BX, 77-5610
 QR DY2& 2U, 77-5445, 77-5517, 77-5518, 77-5519, 77-5520
 77-5753
 QVYZ1R CQ DQ -L, 77-5853
 QVYZ1R DQ, 77-5986
 QVYZ2S2 -DL, 77-5499
 QYVQ, 77-5618
 Q1NUNO&1, 77-5537
 Q2, 77-5451, 77-5782, 77-5943
 Q2K &Q, 77-5706
 Q2M1, 77-5706
 Q2N1&1, 77-5706
 Q4N4&NO, 77-5606, 77-5978
 R, 77-5551, 77-5552
 RR, 77-5485
 SUYZMR, 77-5986
 T B3 G6 E666 COT&&T&J, 77-5543, 77-5545
 T B656 HMJ, 77-5567
 T C566 DO LVOJ BO1, 77-5668, 77-5669, 77-5670, 77-5671
 77-5672
 T C6656 1A P GN LM CUTT&&J G EVM- DT B565 CO
 EVN HVNTJ BQ DY GIY
 77-5577
 T C666 BN ISJ EG B3N1&1, 77-5602

T C666 BO EV INJ D FZ N G- K-/VM- OT5-16- AN FVN
 IVN LVO PVM SVTJ G J KY N RY 2
 77-5546, 77-5628, 77-5741
 T D3 B556 BN EM JV MVTJT&J GO1 H1OVZ KZ L
 77-5627, 77-5629
 T D3 C555 A EO JUTJ AG AG BG GG IG JG KG, 77-5490
 T D36 I666 B6 2AB U EOT&&&&J, 77-5542, 77-5543
 T E3 H6 D6 B666 FOT&T&&&J, 77-5543
 T E6 C6 B655 DO KV PO RO SU&&&TTJ IQ MO1
 77-5510
 T F5 C6 B655 DOV GV OO QO RUT&&TTJ LO1, 77-5406
 77-5506, 77-5507, 77-5508, 77-5509, 77-5510
 77-5511, 77-5512, 77-5513
 T3NTJ A- 3PST3NTJ A- 3PS, 77-5629
 T3OTJ, 77-5489
 T3OTJ B2, 77-5488
 T30TJ, 77-5488
 T30TJ BR, 77-5542
 T5NNVJ A BR& E, 77-5569
 T5NTJ ANO, 77-5603
 T5OJ BNW E- ET5N CSJ BMVH, 77-5464
 T5OV EHJ CQ DQ EYQ1Q, 77-5599, 77-5983
 T5VNNV EHJ BR& CR& E4, 77-5451
 T50J BNW E1UNMVZ, 77-5625
 T50J BYVZU1- BT50J ENW, 77-5462, 77-5463
 T55 AN CUTJ FQ D1OV1- ET5OVTJ C D EQ, 77-5505
 T56 BM DN FN HNJ GZ IO1, 77-5503
 T56 BM DN FN HNJ ISH, 77-5535
 T56 BN DN FNVNVJ B F H, 77-5479, 77-5629, 77-5631
 77-5679
 T56 BO DO CHJ G1U2, 77-5516
 T56 BO DO CHJ G2U1, 77-5516
 T56 BO DO CHJ G3 H1O2O2O4, 77-5602
 T56 BOV GO IU&TJ FQ, 77-5514
 T6MPOTJ BO BN2G2G, 77-5401, 77-5533
 T6MTJ, 77-5602
 T6N DNTJ ANO DNO, 77-5603
 T6N DNTJ AYR&R& D, 77-5602
 T6N DOTJ ANO, 77-5604
 T6NJ BN2N1&1&1- BT5SJ, 77-5602
 T6NTJ ANO, 77-5603, 77-5604
 T6NVMVJ EE A- ET5OTJ B1Q CQ -A&C, 77-5632
 T6NVMVJ EF A- ET5OTJ B1Q CQ, 77-5758
 T6NVMVJ EI A- ET5OTJ B1Q CQ -A&C, 77-5775, 77-5853
 T6NVNJ DZ A- BT5OTJ CQ DQ E1Q, 77-5758
 T6VMVNV FHJ D F F- AL6UTJ, 77-5569
 T6VMVTJ E1YQ- BL6VTJ D F, 77-5986
 T66 BM DN FN HNJ IS- ET5N ONJ DNW, 77-5579

66 BN DN GN JNJ CZ EQ H1MR DVMYVQ2VQ
 77-5466
 66 BNJ BO ENW, 77-5583, 77-5623, 77-5624, 77-5625
 77-5629, 77-5631, 77-5703
 66 BOVJ, 77-5569
 66 BVOT&J D GG IVMYVQ1R& JQ, 77-5515
 66 B6 A B- C 1B I BN DN FN HNTJ, 77-5602
 67 GN JN IHJ CG HM1 JO KR, 77-5602
 HIG, 77-5411
 HR DY, 77-5516
 H1YQYQYQ1Q -BAA -D, 77-5618
 NMYUM&N1&NO, 77-5536, 77-5537, 77-5580, 77-5620
 77-5622, 77-5623, 77-5630, 77-5631, 77-5680
 77-5681, 77-5743
 NR DR, 77-5473
 S1&O1, 77-5401, 77-5626, 77-5627, 77-5629, 77-5990
 S1&O2, 77-5627, 77-5629, 77-5632, 77-5680
 MR, 77-5964
 N1&1, 77-5502
 Q, 77-5504
 R, 77-5478, 77-5479
 R B, 77-5479
 R B DNUNR B, 77-5482
 R B DR B, 77-5473
 R BZ DNW, 77-5435
 R DR DZ, 77-5478
 VMQ, 77-5758
 VN1&NO, 77-5616, 77-5617, 77-5619

ZVN2&NO, 77-5612, 77-5613, 77-5614, 77-5615
 ZVN4&NO, 77-5617
 ZVO2, 77-5497, 77-5498
 ZVO2K &G &5/8, 77-5499
 ZV1U1, 77-5495
 ZY2&1Q, 77-5706
 Z2CN, 77-5983
 Z2Q, 77-5706
 Z3M4M3Z, 77-5976
 Z3M4Z, 77-5976
 Z3Z, 77-5976, 77-5991
 1H, 77-5476
 1MM1, 77-5500, 77-5503, 77-5504
 1MM1 &GH &GH, 77-5501
 1M1, 77-5610
 1N1&R DNUNR, 77-5427, 77-5482
 1N1&R DNUNR C, 77-5480, 77-5481
 1OSWO1, 77-5629
 1UYG1U1, 77-5597
 1U1R, 77-5495
 1U2R DO1, 77-5516
 1VOR BVQ, 77-5451
 1VO1U1, 77-5597
 1X&&R BQ E CX, 77-5610
 2U1R DO1, 77-5516



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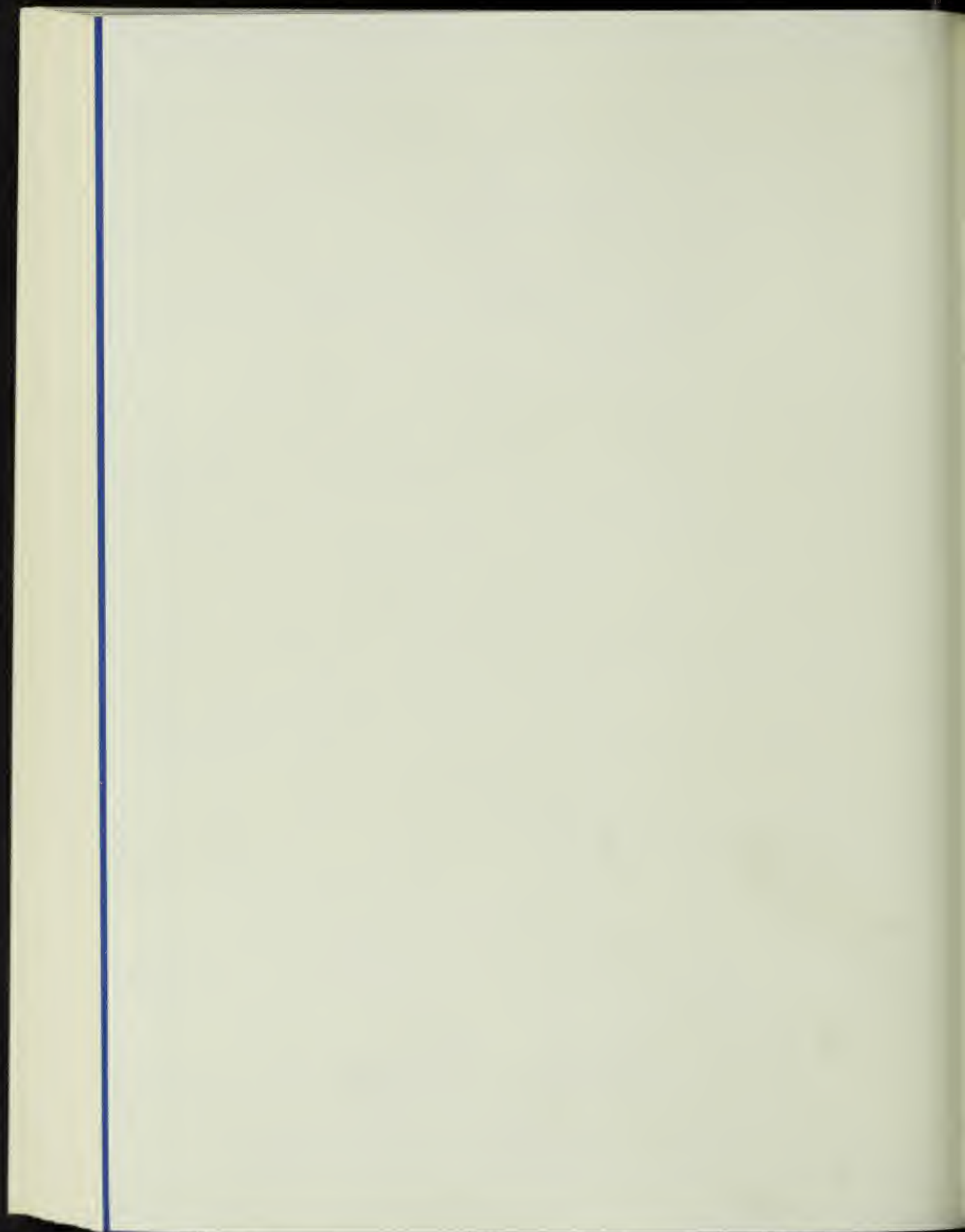
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EDITOR

GEORGE P. STUDZINSKI, M.D., Ph.D.
COLLEGE OF MEDICINE AND DENTISTRY
OF NEW JERSEY, NEWARK

ASSOCIATE EDITOR

JUSSI J. SAUKKONEN, M.D.
JEFFERSON MEDICAL COLLEGE
PHILADELPHIA

NCI STAFF CONSULTANTS

ELIZABETH WEISBURGER, Ph.D.
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BRUCE H. KLEINSTEIN, Ph.D., J.D., *Assistant Director, Biomedical Projects*

RUTHANN E. AUCHINLECK, *Managing Editor*

The Franklin Research Center
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VOLUME 15, ISSUE 11

CONTENTS

	Cross Reference Abbreviations	Article Numbers	Page
REVIEW	(Rev)	77-6001-77-6131	2125
CHEMICAL CARCINOGENESIS	(Chem)	77-6132-77-6298	2148
PHYSICAL CARCINOGENESIS	(Phys)	77-6299-77-6306	2181
VIRAL CARCINOGENESIS'	(Viral)	77-6307-77-6433	2184
IMMUNOLOGY	(Immun)	77-6434-77-6496	2215
PATHOGENESIS	(Path)	77-6497-77-6568	2229
EPIDEMIOLOGY AND BIOMETRY	(Epid-Biom)	77-6569-77-6587	2243
MISCELLANEOUS	(Misc)	77-6588-77-6600	2247
AUTHOR INDEX			2251
SUBJECT INDEX			2259
CHEMICAL ABSTRACTS SERVICE REGISTRY NUMBER INDEX			2325
WISWESSER LINE NOTATION INDEX			2329

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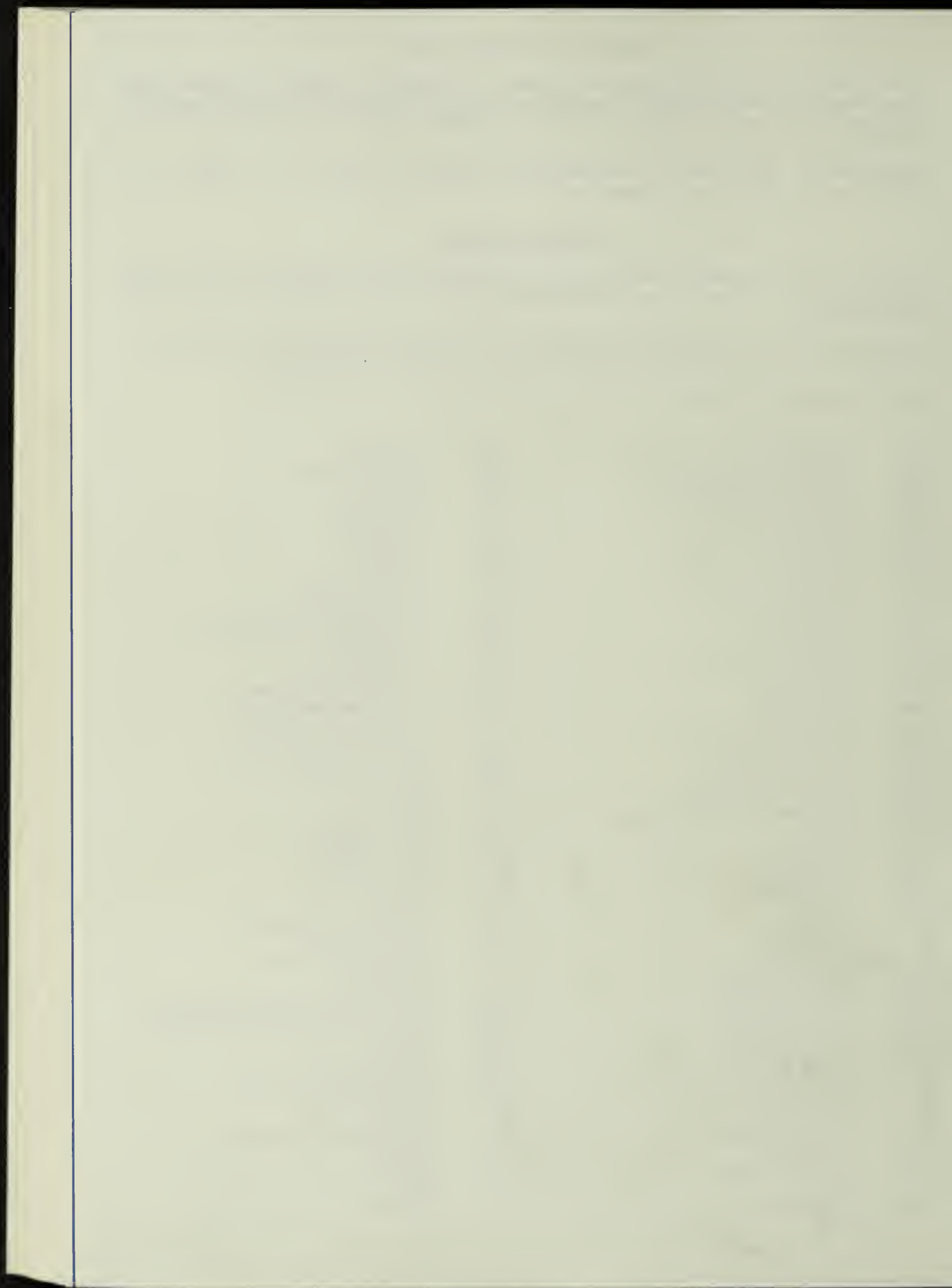
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LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μ l	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μ Ci	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED ₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO ₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μ g	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intra-dermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD ₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intraperitoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD ₅₀	median lethal dose		
M	molar		
μ M	micromolar		



REVIEW

7-6001 **What May Be Learned from Short- and Long-Term Tests and from Studies on Carcinogenicity, Teratogenicity and Mutagenicity?** (Ger.) Froberg, H. (Institut für Toxikologie der Firma E. Merck, Postfach 41 9, 6100 Darmstadt 2, W. Germany). *Arzneim Forsch* 27(2a): 28-241; 1977.

Because of differences in metabolism and sensitivity between animals and humans, animal tests cannot predict with certainty if a compound or drug has side effects in humans. However, new techniques have increased predictability in the last 15 yr. Results from the most commonly used animal tests are compared with findings in humans. The side effects most difficult to detect are systemic hypersensitivity reactions. In toxicologic studies, side effects can appear from or be aggravated by endogenous, biochemical, or morphological factors and the simultaneous administration of other drugs. The effects of direct carcinogens such as nitrogen mustards and ethyleneimine derivatives can be predicted from animal experiments. Teratogenic compounds can act on the mother, on the embryo directly, and on the embryo through the mother. Toxicity in the mother can lead to malnutrition and therefore to embryonic, perinatal, or postnatal defects as a result. In humans some postnatal aberrations are transient. In genetics the two mutation types are gene mutation (DNA in regenerative cells is altered) and chromosomal mutagenesis. Gene mutation cannot be tested in mammals at present. DNA changes are tested in microorganisms; those due to chromosomal mutagenesis, in human lymphocytes. Correlation between mutagenesis and carcinogenesis can be made only for compounds that are metabolized to strongly electrophilic substances. Direct comparisons of mutagenesis between animal experiments and humans are possible by examination of chromosomal mutagenesis. Overall, at present 70% of possible side effects can be predicted from animal experiments. (262 refs.)

7-6002 **Experimental Tumors and Exogenous Agents. Perspectives Opened Up by Experimental Carcinogenesis.** (Ita.) Schiffer, D. (Clinica Neurologica II, Università di Torino, Turin, Italy); Giordana, M. T. *Pathologica* 9(989/990): 125-135; 1977.

Literature on the induction of cerebral tumors by carcinogenic agents, specifically nitrosourea derivatives, in newborn and adult animals and also in fetuses, by the transplacental route, is reviewed. The mechanism by which these compounds are carcinogenic has not yet been defined clearly. It is emphasized that the methyl derivatives are active only in adult animals, but the ethyl derivatives act from the last 5 days of

intrauterine life to the 30th day of extrauterine life. The susceptibility of animals to these compounds, however, decreases in the first month of extrauterine life. A possible involvement of viruses in the chemical induction of tumors cannot be excluded. Induced cerebral tumors are very similar to the spontaneous cerebral tumors in man. An exogenous origin of human cerebral tumors is quite possible, as nitrosourea substances are easily formed in man as a result of primary amines and nitrites present in food and as preservatives, respectively. A low dose that may not be carcinogenic to an adult animal may be so to a fetus. However, it is not clear yet if the same result may occur in a human fetus. (44 refs.)

77-6003 **The Pathogenesis of Experimental Bladder Cancer.** (Eng.) Bryan, G. T. (Dept. Human Oncology, Univ. Wisconsin, Center for Health Sciences, 1300 University Ave., Madison, WI 53706). *Cancer Res* 37(8/part 2): 2813-2816; 1977.

A review of the pathogenesis of N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN)-, braken fern (BF)- and N-[4-(5-nitro-2-furyl)2-thiazolyl]formamide (FANFT)-induced lesions in various species is presented. Usually these lesions are transitional cell carcinomas, with squamous cell carcinomas appearing rarely. Other carcinomas are extremely uncommon. With BBN, rats are more susceptible than mice, hamsters and guinea pigs. With FANFT, rats are more susceptible than mice and hamsters; guinea pigs appear to be resistant to oncogenesis by this compound. With BF, the rat is most susceptible, followed by the guinea pig and mouse. Dogs are susceptible to BBN and FANFT; cows respond to BF. By 10 wk of exposure to FANFT, the bladder epithelium of rats has undergone irreversible changes. The lesions become proliferative, and invasive or metastatic bladder cancer is present in 90% of the animals surviving > 10 wk. Similar observations have been made with BBN and BF. One study recently suggested that hyperplastic lesions induced by FANFT in the rat are reversible up to and through 6 wk providing the carcinogen is removed from the diet. It is suggested that species not capable of acetylating aromatic amines into innocuous molecules are more likely to develop bladder tumors. (28 refs.)

77-6004 **The Natural History of Neoplasia. Newer Insights Into an Old Problem.** (Eng.) Pitot, H. C. (Dept. Oncology, McArdle Lab. Cancer Res., Univ.

Wisconsin Medical Sch., Madison, WI 53706). *Am J Pathol* 89(2): 402-412; 1977.

Liver neoplasia was investigated in animals subjected to partial hepatectomy and a single gastric instillation of diethylnitrosamine (1-30 mg/kg); one group underwent tumor promotion by phenobarbital (0.05% in the diet for 6 mo). A marked increase in the number of enzyme-altered hepatic foci resulted from tumor promotion, and hepatocellular carcinomas were also observed in the phenobarbital-fed group. Biochemical heterogeneity, such as that of developed neoplasms, was seen in the transformed cells at the earliest stage of tumor initiation. These findings suggest that hepatic carcinogenesis is a two stage process. Similar studies from the literature are reviewed. (27 refs.)

- 77-6005 Alkylation Damage and DNA Excision Repair in Mammalian Cells.** (Eng.) Strauss, B. S. (Dept. Microbiology, Univ. Chicago, Chicago, IL 60637); Karran, P.; Higgins, N. P. *J Toxicol Environ Health* 2(6): 1395-1414; 1977.

Excision repair was studied using benzoyleated naphthoylated DEAE cellulose chromatography. RAJI cells were treated with methyl methanesulfonate (MMS, 400 µg/ml) and acetoxy acetylaminofluorene (AAAF, 200 µg/ml). While approximately equal numbers of lesions were produced at these doses, the max rate of repair was greater in cells treated with AAAF than in those treated with MMS; MMS was able to induce DNA strand interruptions, while AAAF was not. Differences between strand breaks induced by comparable doses of x-irradiation and MMS were attributed to metabolically produced gaps in the MMS group. The differences between repair of AAAF- and MMS-induced damage were much less in unstimulated cells than in those in cycle, suggesting a general relationship between replication competence and repair activity. In studies with chick reticulocytes, as opposed to the repair competent RAJI cells, there was no difference in the max repair activity induced by the two agents. Larger repair patch size was observed for AAAF-induced damage in contrast to that induced by MMS. It is concluded that there are different pathways for the repair of MMS-type and AAAF-type damage. Furthermore, some replicating cells appear unable to repair MMS-induced changes. (36 refs.)

- 77-6006 Nucleic Acid Alkylation, Mutation and Carcinogenesis: Is There a Relationship?** (Eng) Singer, B. (Dept. Molecular Biology, Univ. California, Berkeley, CA 94720). *Trends Biochem Sci* 2(3): 180-183; 1977.

The possible association among the O-alkylation of nucleic acids, mutation, and cancer is discussed based on a review of recent data. O-Alkylation may be associated with carcinogenesis, as most carcinogenic alkylating agents react mainly

with oxygen; there is a high probability that this reaction is also mutagenic. Alkylating reactions occurring elsewhere in the cell may influence carcinogenesis, but the initiating event is likely to be a genetic alteration of DNA due to mutation. (25 refs.)

- 77-6007 Inducible Pathways in Deoxyribonucleic Acid Repair, Mutagenesis and Carcinogenesis.** (Eng.) Radman, M. (Departement de Biologie Molculaire, Université Libre de Bruxelles, B1640, Rhode St. Genese, Belgium). *Biochem Soc Trans* 5(4): 1194-1199; 1977.

Current knowledge and ideas about the genetic control and molecular mechanisms of mutagenesis in bacteria, including the SOS repair system, are summarized in relation to possible mechanisms of malignant transformation in mammalian cells. A single-locus model for malignant transformation through mutagenesis is discussed and correlated with the significance of increased plasminogen activator activity. (35 refs.)

- 77-6008 Recent Progress in Chemical Carcinogenesis** (Eng) Daudel, R. (Centre de Mécanique Ondulatoire Appliquée, 75019, Paris, France). *Int J Quantum Chem Quantum Biol Symp* (4): 169-177; 1977.

During a 1976 symposium held in Menton, France, the process of chemical carcinogenesis from the molecular to the animal level was examined. Some of the main results presented are summarized under the following headings: interaction of carcinogens with DNA and resulting damages, repair of damaged DNA, mutagenesis and transformation, and the role of DNA repair in mutagenesis and chemical carcinogenesis (12 refs.)

- 77-6009 Extrapolation of Cellular and Molecular Level Studies to the Human Situation.** (Eng.) Magee, P. N. (Fels Res. Inst., Temple Univ. Sch. Medicine, Philadelphia, PA 19140). *J Toxicol Environ Health* 2(6): 1415-1424; 1977.

The extrapolation of cellular and molecular level studies to humans in the areas of carcinogenesis and mutagenesis is discussed. In view of the large number of confirmed and suspected chemical carcinogens observed in animal systems and the relatively small number of recognized carcinogens for humans, several parameters that may have predictive value are considered. One index of carcinogenic potential is chemical structure. Groups of chemical compounds that are presumed to contain carcinogenic members include polycyclic hydrocarbons, aromatic amines, aromatic azo compounds, nitrosamines,

amines, aflatoxins, chlorinated hydrocarbons, and nitrofurans. Most chemical carcinogens are themselves inactive and require metabolic conversion by microsomal mixed-function oxidases or other enzymes to their active forms--the ultimate carcinogens. All ultimate carcinogens recognized so far are electrophiles that react with nucleophilic sites, presumably on nucleic acids and proteins. Identification of carcinogen adducts with human macromolecules may be used as an index of carcinogenic potential. Two other tests for chemical carcinogens are *in vitro* assays for mutagenesis in microbial or mammalian cells and cellular transformation *in vitro*. A more recent test is measurement in the intact animal of DNA repair induced by the suspected carcinogen. (44 refs.)

77-6010 Cutaneous Carcinogenesis. (Eng) Bock, F. G. (Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY). In: *Dermatology and Pharmacology*. Marzulli, F. N.; Maibach, H. I., eds. (Washington: Hemisphere Publishing Corporation): *Advances in Modern Toxicology*. Vol. 4, 567 pp.: 473-485; 1977.

A review of cutaneous carcinogenesis in humans and animals revealed that the most likely carcinogens for humans and animals are those agents that are transformed in the skin to their active forms; those that must be activated elsewhere or active forms administered *sc* are less likely to cause cancer. Furthermore, agents that are inactive in laboratory animals may be carcinogenic to man, and carcinogens at weak or sub-threshold levels may act as co-carcinogens. (56 refs.)

77-6011 Rapid Methods for Determining the Carcinogenicity of Chemical Compounds. (Rus) Belitskii, G. A. (Lab. Chemical Carcinogenesis, Oncological Res. Center, USSR Acad. Medical Sciences, USSR). *Vopr Onkol* 23(9): 90-96; 1977.

Methods suitable for rapid testing of chemical carcinogenicity are outlined. Analysis of covalent bonding with cellular macromolecules, DNA repair synthesis, mutagenicity and *in vitro* cell transformation can be used to screen potential carcinogens. (48 refs.)

77-6012 Screening of Potential Chemical Carcinogens by Means of Mammalian Cells in Vitro. (Eng) Thust, R. (Pathological Inst. of the Medical Acad. Erfurt, Erfurt, E. Germany). *Arch Geschwulstforsch* 46(7): 538-548; 1976.

A survey of the development of screening systems to detect carcinogenicity of chemical compounds with mammalian

cells *in vitro* is presented. One method uses host-mediated assays, a combination of carcinogen application into intact animals (possibly pregnant animals) and succeeding explanation of organs or establishment of cell cultures from fetuses following transplacental action of the compound tested. The compound is metabolized within the organism, thus bypassing critical problem of metabolic competence of cultured cells. The second method is direct application of the carcinogen into cell cultures. Besides using fresh embryonic cells, there is an increasing tendency to use established cell lines with a strict postconfluence inhibition of proliferation and an extremely low background of spontaneous alteration *in vitro*. Possibilities for the metabolism of the carcinogens in cell cultures are pointed out, and the value of 'indicators' of carcinogen-induced alterations in relation to neoplastic properties is discussed. The literature published indicates that cell cultures offer the possibility for early detection of potentially carcinogenic agents. (50 refs.)

77-6013 Method of Calculation of the Effective Dose and Concentration of Chemical Carcinogenic Agents. (Rus) Kurliandskii, B. A. (Municipal Sanitary-Epidemiological Center, Moscow, USSR); Nevzorova, N. I. *Vopr Onkol* 23(9): 59-62; 1977.

Probit analysis according to Litchfield and Wilcoxon is recommended for the calculation of the effective carcinogenic doses and concentrations (BD16, BD50, BD84) of various chemical carcinogens. Examples and values are presented for N,N'-dinitrosodimethylethylene diamine, benzo(a)pyrene, 1,2,5,6-dibenzoanthracene, 2-amino-5-azotoluene and vinyl chloride. (17 refs.)

77-6014 Toxicology of Environmental Arsenic. (Eng) Fowler, B. A. (Environmental Toxicology Branch, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC). In: *Advances in Modern Toxicology*. Goyer, R. A.; Mehlman, M. A., eds. (New York: John Wiley & Sons): Vol. 2, *Toxicology of Trace Elements*, pp. 79-122; 1977.

The environmental toxicity of arsenic is reviewed. Binding of arsenic by the blood shows species variation. In the leukemic blood of humans, arsenic is concentrated in the WBC and plasma. Ingested arsenic results in gastrointestinal damage, convulsions, and hemorrhage; acute inhalation of arsine gas causes death from renal failure. Cellular toxicity is attributed to the inhibition of cellular respiration. Several human and animal studies are surveyed. (266 refs.)

77-6015 Polybrominated Biphenyl (PBB) Toxicosis: An Environmental Accident. (Eng) Getty, S. M.

(Coll. Veterinary Medicine, Michigan State Univ., East Lansing, MI); Rickert, D. E.; Trapp, A. L. *CRC Crit Rev Environ Control* 7(4): 309-323; 1977.

Accidental feeding of fireMaster BP-6, a polybrominated biphenyl (PBB), to various farm animals resulted in a decreased food consumption and lack of wt gain in most species and hematoma development in cows. Octabromobiphenyl administration to laboratory animals has resulted in liver enlargement and thyroid hyperplasia in rats. Findings on the excretion of PBBs and their fate in the soil are reviewed. (50 refs.)

77-6016 The Carcinogenicity of Automobile Exhausts, from Data Obtained in the USSR. (Eng) Shabad, L. M. (Cancer Res. Center, Acad. Medical Sciences USSR, Kashirskoye Shosse 6, Moscow 115478, USSR). *IARC Sci Publ* (16): 61-67; 1977.

Studies carried out over a 20-yr period on the carcinogenicity of polycyclic aromatic hydrocarbons (PAH), particularly benzo(a)pyrene (BP), in automobile exhausts are reviewed. Benzene extracts of soot from cars with a carburetor or a diesel engine were applied to the skin of mice. The extracts of carburetor soot (containing 200 µg/g BP) produced a high incidence of papillomas and carcinomas, but the diesel soot extracts (1 µg/g BP) caused none. Tumor appearance, therefore, corresponded to the BP content of the soot. Tests with platinum ball neutralizers, additives to diesel fuel, adjusting the rarefying regulator, and the replacement of spark ignition by a forcamera-torch system indicate that it is possible to reduce the discharge of carcinogenic hydrocarbons into the atmosphere considerably. Discharges from factories and heating systems and from airplane engines also contribute to the atmospheric PAH load. Studies on engines operated at constant levels and at the Europa drive cycle show that one car discharges about 600 µg BP/working hr, which amounts to > 1 kg/yr. Measures aimed at decreasing the PAH in automobile exhausts, therefore, are necessary to create purer air in cities. (23 refs.)

77-6017 Influence of Environmental Factors on the Respiratory Tract. Summary and Perspectives. (Eng) Dannenberg, A. M. (Dept. Environmental Health Sciences, Johns Hopkins Sch. Hygiene and Public Health, Baltimore, MD 21205). *J Reticuloendothel Soc* 22(3): 273-290; 1977.

In a review of toxic environmental agents, major carcinogens are tabulated; and pulmonary defense mechanisms, macrophage function, respiratory infections, allergic pulmonary reactions, and synergism among these agents are examined. Further work is needed to establish safe levels of exposure to these compounds. (86 refs.)

77-6018 Effects of Environmental Chemicals on the Genetic Regulation of Microsomal Enzyme Systems. (Eng) Nebert, D. W. (Room 13-N-234, Bldg. 10, Natl. Inst. Child Health and Human Development, Bethesda, MD 20014); Levitt, R. C.; Orlando, M. M.; Felton, J. S. *Clin Pharmacol Ther* 22(5,part 2): 640-658; 1977.

Examples of the interaction of environmental carcinogens (polycyclic hydrocarbons, halogenated hydrocarbons, 2-acetylaminofluorene and acetaminophen) with the genetic regulatory system controlling the monooxygenase response are presented. Studies have indicated that because of the small number of genes involved in a chemical's metabolism, an individual's response to a given environmental chemical can vary, even among siblings. (79 refs.)

77-6019 Role of the National Cancer Institute in the National Cancer Program on Environmental Carcinogens. (Eng) Flamm, W. G. (Div. Cancer Cause and Prevention, NCI, Bethesda, MD 20014). *Ann NY Acad Sci* 298: 593-594; 1977.

Under the auspices of the NCI, environmental carcinogenesis is one of the more nationally publicized cancer prevention efforts. Environmental carcinogenesis is being dealt with through the National Cancer Program, which was created by the National Cancer Act, the Smoking and Health Program for cigarette smoking and bronchogenic cancer, and the Diet and Nutrition Program. Many of the studies are concerned with water-borne carcinogens. (no refs.)

77-6020 Rationale Developed by the Environmental Protection Agency for the Assessment of Carcinogenic Risks. (Eng) Albert, R. E. (Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY 10016); Train, R. E.; Anderson, E. *J Natl Cancer Inst* 58(5): 1537-1541; 1977.

The approach adopted by the Environmental Protection Agency (EPA) for the assessment of health risks from environmental carcinogens is described. This approach is embodied in the EPA's "Interim Guideline for Carcinogen Risk Assessment," an operational document that sets up the rationale and general framework for interpreting carcinogenesis data for regulatory usage. Evaluation of the evidence regarding suspect carcinogens includes judgements on the quality and adequacy of data, the likelihood that the agent is a human carcinogen, and an estimate of the magnitude of the cancer burden that could be expected from the agent if no regulatory action were taken. According to the guideline, any evidence of tumorigenic activity in animals is a signal that the agent is a potential human carcinogen. In the few instances in which quantitative comparisons can be made between ani-

ls and humans, the magnitude of the carcinogenic response in the most sensitive animals tested shows a reasonable comparability to that of humans. Extrapolation based on near dose-response relationship indicates that a safe level carcinogen exposure is nonexistent. The EPA guideline and the report issued by the National Cancer Advisory Board's Subcommittee on Environmental Carcinogens agree on the interpretation of carcinogenesis data. Portions of the guideline that relate to risk assessment are included in Appendix. (3 refs.)

-6021 **Keynote Address.** (Eng) Lord, M. W. (U.S. District Court Minnesota, Minneapolis, MN 55401). *Ann NY Acad Sci* 298: 201-209; 1977.

the legal aspects of environmental pollution of the Great Lakes are discussed. Courts should be made aware of the potential carcinogenic hazards of industrial waste products. (no refs.)

-6022 **General Discussion.** (Eng) McCabe, L. J. (Health Effects Res. Lab., U.S. Environmental Protection Agency, Cincinnati, OH 45268). *Ann NY Acad Sci* 298: 90-103; 1977.

aspects of water pollution control in the U.S. are discussed including sewage treatment, agricultural contamination from fertilizers and pesticides, and industrial waste. Compounds found in drinking water are tested for carcinogenicity and/or mutagenicity and chronic toxicity by use of the Ames test, the *Saccharomyces* yeast assay, the in vivo teratology bioassay in the rat, and a neonatal rat bioassay. (13 refs.)

-6023 **General Discussion.** (Eng) Dawe, C. J. (NCI, Bethesda, MD 20014). *Ann NY Acad Sci* 298: 16-329; 1977.

the occurrence of neoplasms, particularly lip papillomas, in aquatic animals is discussed. Problems in establishing the etiology of the neoplasms and their potential use as indicators of environmental carcinogens are noted. (no refs.)

-6024 **Metabolism of Aromatic Hydrocarbons in Marine Organisms.** (Eng) Malins, D. C. (Northwest and Alaska Fisheries Center, Natl. Oceanic and Atmospheric Admin., Natl. Marine Fisheries Service, Seattle, WA 98112). *Ann NY Acad Sci* 298: 482-496; 1977.

Data on the metabolism of aromatic hydrocarbons by marine organisms are reviewed, with emphasis on the enzyme activity involved and the nature of the breakdown products formed. The influence of other chemical pollutants (eg, polychlorinated biphenyls, nitrosamines and trace metals) on enzyme activities in marine animals is also discussed. (42 refs.)

77-6025 **Occurrence and Fate of Organic and Inorganic Contaminants in Marine Animals.** (Eng) Whittle, K. J. (Torry Res. Station, Aberdeen, Scotland); Hardy, R.; Holden, A. V.; Johnston, R.; Pentreath, R. J. *Ann NY Acad Sci* 298: 47-79; 1977.

Several reports in this monograph illustrate the significance of chemical contaminants in producing biologic effects in aquatic organisms. Hydrocarbons, organochlorine and organophosphorus pesticides (including DDT and the polychlorinated biphenyls), miscellaneous organics such as tetrachloroethane and carbon tetrachloride, toxic metals such as lead, cadmium, and zinc, and polluting radionuclides are among the chemical species discussed. (137 refs.)

77-6026 **General Discussion.** (Eng) Tardiff, R. G. (Health Effects Res. Lab., U.S. Environmental Protection Agency, Cincinnati, OH 45268). *Ann NY Acad Sci* 298: 190-200; 1977.

Problems in the use of animal models to screen for potentially carcinogenic environmental chemicals are discussed. Mutagens produced by the degradation of oil and by chlorination and ozonation treatments of drinking water are considered.

77-6027 **Are Cities Doing Enough to Remove Cancer-causing Chemicals from Drinking Water?** (Eng.) Dallaire, G. (Editorial Dept., Civil Engineering, 345 E. 47th St., New York, NY 10017). *Civ Eng (NY)* 47(7): 88-94; 1977.

Various perspectives and data on whether or not carcinogens in the drinking water are a significant threat to consumer health are reviewed. Means of removing these carcinogens from the drinking water supply and the cost to the consumer are discussed. (no refs.)

77-6028 **Postcoital Administration of Diethylstilbestrol.** (Fre.) Polderman, J. (Rue Van den Corput 47, Forest, B 1180 Brussels, Belgium). *Nouv Presse Med* 6(11): 953-955; 1977.

The mechanism of action; efficacy; contraindications; im-

mediate, teratogenic, and secondary toxic effects; and dose/regimen of diethylstilbestrol (DES) for use as a postcoital contraceptive are reviewed. High dosages of estrogen administered postcoitally are thought to prevent implantation of the zygote. Literature data on 6,907 women who took DES for this purpose show a failure rate of 5.1%; possible contributing factors are discussed. Nausea, vomiting, headache, vaginal perturbations, and irregular menses were expected side effects in 50%-60% of the subjects. It is suggested that, because of the possibility of long-term negative side effects (eg, increased risk of carcinoma in daughters), DES as a "morning after" contraceptive be prescribed only for exceptional cases. (22 refs.)

- 77-6029 **Squamous Cell Neoplasia Controversy in the Female Exposed to Diethylstilbestrol.** (Eng.) Robboy, S. J. (Dept. Pathology, Harvard Medical Sch., Boston, MA 02115); Prat, J.; Welch, W. R.; Barnes, A. B. *Hum Pathol* 8(5): 483-485; 1977.

The present data do not suggest that the risk of squamous cell dysplasia and carcinoma of the cervix and vagina in diethylstilbestrol exposed women is as great as was originally expected. Although vaginal dysplasia does appear to be more frequent in the exposed women, further studies are necessary to determine the actual risk of cancer. It is emphasized that immature squamous metaplasia, which occurs frequently, is distinct from precancerous dysplasia and carcinoma. In addition, atypical or malignant columnar cells can be mistaken for dysplastic or malignant squamous cells. (13 refs.)

- 77-6030 **Estrogen Treatment of Postmenopausal Women. Benefits and Risks.** (Eng.) Shoemaker, E. S. (Cecil H. and Ida Green Center for Reproductive Biology Sciences, Univ. Texas Southwestern Medical Sch., Dallas, TX 75235); Forney, J. P.; MacDonald, P. C. *JAMA* 238(14): 1524-1530; 1977.

Estrogen treatment of postmenopausal women may not increase the incidence of breast tumors in these women, but it is known that such treatment does not prevent these tumors. Furthermore, estrogen treatment, or increased endogenous production of estrogen, is associated with an increased risk of endometrial carcinoma. Other dangers as well as benefits of estrogen treatment in postmenopausal women are reviewed. (65 refs.)

- 77-6031 **Endometrial Cancer after Menopausal Use of Estrogens.** (Eng.) Greenwald, P. (New York State Dept. Health, Cancer Control Bureau, Albany, NY);

Caputo, T. A.; Wolfgang, P. E. *Obstet Gynecol* 50(2): 239-243; 1977.

Epidemiological evidence indicates an association between estrogen use and endometrial cancer. Estrogen use in the US has roughly quadrupled from 1962 to 1975. The New York State Cancer Registry data show a 68% increase in the incidence of endometrial cancer during the period 1960-1974, with 82% of the increase occurring over the last 5 yr. Several previous studies found an approx 7.5- to 8.0-fold increased risk of endometrial cancer due to estrogen use (compared to nonusers). (22 refs.)

- 77-6032 **Oestrogen Treatment and Endometrial Carcinoma (Letter to Editor).** (Eng.) Guillebaud, J. (Nuffield Dept. Obstetrics and Gynaecology, John Radcliffe Hosp., Headington, Oxford, England). *Br Med J* 2(6093): 1025; 1977.

The association between estrogens and endometrial carcinoma requires further investigation. In women with postmenopausal or undiagnosed irregular genital bleeding, estrogen treatment is contraindicated; therefore, endometrial carcinoma diagnosed later in these women is not likely to be connected to estrogen therapy. Injudicious prescribing of estrogens in such cases as these would be a dangerous reaction against undue restraint of estrogen use. (no refs.)

- 77-6033 **Estrogens and Endometrial Carcinoma.** (Eng.) Scully, R. E. (Dept. Pathology, Massachusetts General Hosp., Harvard Medical Sch., Boston, MA 02115) *Hum Pathol* 8(5): 481-483; 1977.

The literature linking estrogens with endometrial carcinoma is reviewed. The data indicate that the risk of cancer is not as great as previously reported; one reason could be that cases of reversible atypical hyperplasia were included as "cancers". A high proportion of carcinomas associated with estrogen administration are of a low order of malignancy and carry an excellent prognosis. (15 refs.)

- 77-6034 **Importance of Secretory Mechanisms in Assessing the Potential Carcinogenic Hazard of Exogenous Estrogens.** (Eng.) Greenman, D. L. (Div. Molecular Biology, Natl. Center Toxicology Res. Jefferson, AR 72079). *J Toxicol Environ Health* 3(1/2): 59-60; 1977.

Although the carcinogenic potential of exogenous estrogens taken as contraceptives or for menopausal symptoms has been investigated, little is known of the effects of residues left

meats following treatment of animals with estrogens (eg, ethylstilbestrol). The mechanisms regulating concentrations of circulating endogenous hormones should be examined in order to assess the risk of exogenous compounds which could act by affecting these mechanisms. (5 refs.)

7-6035 **Metabolism of Ethynyl Estrogens.** (Eng.) Helton, E. D. (Natl. Center Toxicological Res., Jefferson, AR 72079); Goldzieher, J. W. *J Toxicol Environ Health* 3(1/2): 231-241; 1977.

The distribution, urinary metabolites and metabolic pathways of ethynylated estrogens are reviewed. Estrogen hepatotoxicity is discussed with respect to the known occurrence of estrogen oxidative metabolism and covalent binding. The effect of removal of the 17 α -ethynyl group on hepatotoxicity is considered. (1 ref.)

7-6036 **Contraceptive Steroids and Liver Lesions.** (Eng.) Garcia, C. R. (Dept. Obstetrics and Gynecology, Univ. Pennsylvania Hosp., Philadelphia, PA 19104); Gordon, J.; Drill, V. A. *J Toxicol Environ Health* 1(1/2): 197-206; 1977.

A review of the studies linking contraceptive steroids with liver lesions indicated that the risk of such lesions is low, particularly when compared with the risks of pregnancy. Better means of investigating the effects of new compounds are needed. Some environmental hepatotoxins are also mentioned. (53 refs.)

7-6037 **The Pharmacodynamics and Toxicology of Steroids and Related Compounds.** (Eng.) Bischoff, J. (Santa Barbara Cottage Hosp. Res. Inst., Santa Barbara, CA); Bryson, G. *Adv Lipid Res* 15: 61-157; 1977.

The role of steroids and related compounds in evaluating the carcinogenicity of a substance, the pharmacodynamics and toxicity of these compounds as contraceptives and food products, and their transplacental and CNS effects are reviewed. Related physiologic mechanisms, enzyme behavior transport mechanisms and side effects are also considered. (538 refs.)

7-6038 **Minireview: The Beagle Dog and Contraceptive Steroids.** (Eng.) Briggs, M. (Sch. Sciences Deakin Univ., Geelong, Victoria, Australia). *Life Sci* 21(3): 275-284; 1977.

Because, in a long-term toxicity study of the oral contracep-

tive ethynone, only beagle dogs developed mammary tumors among the species tested, the US Food and Drug Administration made the beagle the mandatory breed for testing oral contraceptives. Mammary tumor formation in beagle bitches is induced by some progestogens, including progesterone, but not in other laboratory species such as rodents and monkeys. Most tumors are of the benign mixed type, although a small minority are malignant. The latter appear to arise from benign tumors, and they may metastasize as carcinomas or show sarcomatous transformations. The number of carcinomas and sarcomas arising de novo in clinically healthy glands is unknown. Current evidence indicates that oral contraceptives have a protective effect on the occurrence of breast neoplasms in women. Therefore, the beagle findings are irrelevant to the human situation. Possible reasons for the unique response of the beagle to progestogens are discussed. (52 refs.)

77-6039 **Activation Mechanisms in Chlorinated Aliphatic Compounds. Experimental Possibilities and Clinical Significance.** (Ger.) Henschler, D. (Toxikologisches Institut der Universität, Koellikerstr. 2, 8700 Würzburg, W. Germany). *Arzneim Forsch* 27(9b): 1827-1832; 1977.

Asymmetric chlorinated ethylenes (tri-1,1-dichloroethylene and vinyl chloride) are mutagenic in a modified Ames test system whereas symmetrically substituted molecules are inactive. These differences are attributed to the electron withdrawal effect of chlorine in the asymmetric molecules. The in vivo and in vitro rearrangement mechanisms in the biotransformation of these compounds are outlined. (20 refs.)

77-6040 **Chlorinated Dibenzodioxins.** (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*. International Agency for Research on Cancer. (Lyon, France): Vol. 15, pp. 41-102; 1977.

The information available on the toxicity, teratogenicity, mutagenicity, and carcinogenicity of several chlorinated dibenzodioxin derivatives, especially 2,3,7,8-tetrachlorodibenzo-dioxin (TCDD), is reviewed. Because of the inadequacy of studies on the carcinogenicity of these substances, no final evaluation can be made. However, po administration of 2,4,5-trichlorophenoxyethanol and TCDD to Swiss H/Riop mice did increase the incidence of liver tumors in males. A review of the data on human exposure revealed an increased proportion of liver cancers in cancer patients in Hanoi, North Vietnam, after the spraying of herbicides containing TCDD was instituted. A number of cancer cases have

been reported in workers occupationally exposed to TCDD, but the data are not sufficient for a thorough evaluation of the risk to man. The physical and chemical properties of the derivatives are reviewed. (174 refs.)

77-6041 Ethylene Dibromide. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* (Lyon: International Agency for Research on Cancer): Vol. 15, pp. 195-209; 1977.

The experimental evidence on the carcinogenicity of ethylene dibromide is reviewed. When the compound was administered po to (C57Bl x C3H)F₁ mice and Osborne-Mendel rats, squamous cell carcinomas of the forestomach were noted. Ethylene dibromide injected ip in rats induced damage to the spermatogenic cells; however, no data on embryotoxicity or teratogenicity are available. Mutations were induced in *Neurospora crassa* and *Drosophila melanogaster* receiving the compound. Ethylene dibromide has been shown to be toxic to man, but no data are available on its carcinogenicity in humans. (62 refs.)

77-6042 Dihydroxybenzenes. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* (Lyon: International Agency for Research on Cancer): Vol. 15, pp. 155-175; 1977.

The data on the carcinogenicity of catechol, resorcinol and hydroquinone are reviewed. In skin painting studies with female ICR/Ha Swiss mice, catechol increased the carcinogenic effects of benz[a]pyrene. In other mouse experiments, hydroquinone in cholesterol pellets increased the incidence of bladder carcinomas. The LD50s of the chemicals are listed; no data on embryotoxicity or teratogenicity were available for analysis. These findings do not permit an accurate evaluation of carcinogenicity for any of these compounds. The toxic and allergenic effects of these compounds in man are listed; no data are available on human carcinogenicity. (52 refs.)

77-6043 1,4-Bis(chloromethoxymethyl)benzene. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* (Lyon: International Agency for Research on Cancer): Vol. 15, pp. 37-40; 1977.

The carcinogenicity of 1,4-bis(chloromethoxymethyl)benzene, as it was examined in ICR/Ha mice, is reviewed. Cutaneous application and sc administration of this chemical resulted in papillomas, carcinomas, and sarcomas at the site of administration. No epidemiological data on human exposure are available. (1 ref.)

77-6044 1,2-Dibromo-3-chloropropane. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* (Lyon: International Agency for Research on Cancer): Vol 15, pp. 139-147; 1977.

1,2-Dibromo-3-chloropropane produced squamous cell carcinomas in the forestomach of both (C57Bl x C3H)F₁ mice and Osborne-Mendel rats which received the carcinogen po. Furthermore, mammary carcinomas were evident in rats receiving the carcinogen. No human case reports or epidemiological data were available for review. (28 refs.)

77-6045 1,2,3-Tris(chloromethoxy)propane. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* (Lyon: International Agency for Research on Cancer): Vol 15, pp. 301-305; 1977.

The experimental data on the carcinogenicity of 1,2,3-tris(chloromethoxy) propane are reviewed. Cutaneous exposure in ICR/Ha mice resulted in skin papillomas; sc and ip injection resulted in malignant tumors at the site of injection. No human reports or epidemiological data were available for analysis. (4 refs.)

77-6046 trans-1,4-Dichlorobutene. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* (Lyon: International Agency for Research on Cancer): Vol 15, pp. 149-154; 1977.

The carcinogenicity of *trans*-1,4-dichlorobutene has been tested in ICR/Ha Swiss mice given the compound po, sc and ip. Low incidences of local sarcomas were noted in the sc and ip studies, but these results do not permit conclusive evaluation of carcinogenicity. No human epidemiological data were available for review. (11 refs.)

77-6047 1,2-Bis(chloromethoxy)ethane. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*. (Lyon: International Agency for Research on Cancer): Vol. 15, pp. 31-35; 1977.

The experimental data on the carcinogenicity of 1,2-bis(chloromethoxy)ethane are reviewed. Experiments with cutaneous application and sc and ip injection in female ICR/Ha mice resulted in tumor formation at the site of application or injection. No epidemiological data on human cases are available. (12 refs.)

77-6048 Dimethoxane. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*. (Lyon: International Agency for Research on Cancer): Vol 15, pp. 177-181; 1977.

The carcinogenicity of dimethoxane is reviewed based on experimental results in male Wistar rats. After po ingestion of approx 237 g/animal, malignant tumors, predominantly in the liver, were noted. No data on the human cancer risk following dimethoxane exposure were available. (7 refs.)

77-6049 para-Quinone. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*. (Lyon: International Agency for Research on Cancer): Vol 15, pp. 255-264; 1977.

Experimental data on the carcinogenicity of para-quinone are reviewed. In experiments involving cutaneous, inhalation, and sc exposure, carcinomas were noted; but the number of animals involved was insufficient for a conclusive analysis. No data on embryotoxicity or teratogenicity were available. Toxic reactions in man include skin changes and vision disturbances, but no carcinogenic data were available. (31 refs.)

77-6050 Mirex. An Overview. (Eng) Waters, E. M. (Toxicology Information Response Center, Biomedical Sciences Section, Information Center Complex/Information Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Huff, J. E.; Gerstner, H. B. *Environ Res* 14(2): 212-222; 1977.

Carcinogenicity studies are included in this general review of the insecticide mirex (1,1a,2,2,3,3a,4,5,5,5a5b, 6-dodecachlorooctahydro -1,3,4,- metheno-1H- cyclobuta-[cd]pentalene). One hundred four rats were fed mirex (100 or 50 ppm in diet) for 18 mo. Liver changes ranged from fatty metamorphosis and megalocytosis of hepatocytes, cystic degeneration and necrosis, and biliary hyperplasia with periportal fibrosis to neoplastic nodules and hepatocellular carcinoma. The carcinoma occurred in only six animals. (56 refs.)

77-6051 2,4,5-T and Esters. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-d and 2,4,5-T Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*. (Lyon: International Agency for Research on Cancer): Vol. 15, pp. 273-299; 1977.

A review of the experimental results on 2,4,5-trichlorophenoxy)acetic acid (2,4,5-T) is presented. Po and sc administration of the compound did not allow a thorough evaluation of carcinogenicity, although an increase in tumors was noted in one group of mice who received 2,4,5-T po. Teratogenic and embryogenic effects have been observed in mice and rats. One study of exposure to many herbicides, including 2,4,5-T, indicated a two-fold risk of all cancers in exposed workers; but because of the combination of compounds, a specific evaluation cannot be made. Toxic effects on humans are also reviewed. (89 refs.)

77-6052 2,4-D and Esters. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals*. (Lyon: International Agency for Research on Cancer): Vol. 15, pp. 111-138; 1977.

The results of experiments with rats and mice in which (2,4-dichlorophenoxy)acetic acid (2,4-D) was given po, and of those in mice receiving sc injections, are reviewed. Although an increase in the numbers of tumors was noted in rats receiving the compound po and mice receiving its isooctyl ester sc, no evaluation of carcinogenicity can be made due to the small numbers of animals used or to inadequate reporting. The results of further studies on teratogenicity, embryotoxicity and mutagenicity are reported. The results of human epidemiologic studies are not sufficient for evaluating the carcinogenicity of 2,4-D to man. (100 refs.)

77-6053 New Toxic, Irritant and Cocarcinogenic Diterpene Esters from Euphorbiaceae and from

Thymelaeaceae. (Eng) Hecker, E. (Inst. Biochemistry, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany). *Pure Appl Chem* 49(9): 1423-1431; 1977.

The biologically active substances that have been isolated from Euphorbiaceae and Thymelaeaceae are derivatives of three chemically related diterpene parent hydrocarbons: the tetracyclics tiglane and ingenane and the tricyclic daphnane. The naturally occurring polyfunctional diterpene parent alcohols phorbol, ingenol, and resiniferonol are related structurally to these hydrocarbons. The toxic and irritant principles are esters of the parent alcohols, or orthoesters in the case of daphnane. Besides the active derivatives, a number of biologically inactive esters of new macrocyclic diterpenes, eg, lathyrol esters, have been isolated and structurally elucidated. Macrocyclics of this type may be considered intermediates in the biogenesis of the diterpene parents of the active derivatives. Most of the irritant esters also exhibit cocarcinogenic or tumor-promoting activity in mouse skin. Therefore, these diterpene esters may pose a carcinogenic risk for humans. Recently, some of the diterpene esters have been reported to exhibit antileukemogenic activity. (29 refs.)

77-6054 Isopropyl Alcohol and Isopropyl Oils. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* (Lyon: International Agency for Research on Cancer): Vol. 15, pp. 223-243; 1977.

A review of studies to examine the carcinogenic potential of isopropyl alcohol and isopropyl oils is presented. Studies with cutaneous applications in mice allowed no evaluation of risk. An increased incidence of lung tumors was noted in mice following inhalation or sc injection of isopropyl oils formed during the strong-acid process, but no evaluation can be made due to limitations in the studies. Human exposure data indicate that an excess risk of cancers of the paranasal sinuses is connected with manufacture of isopropyl alcohol by the strong-acid process, with isopropyl oils formed as a by-product. An excess risk of laryngeal cancer may also exist for these workers. (71 refs.)

77-6055 Eosin and Eosin Disodium Salt. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* (Lyon: International Agency for Research on Cancer): Vol 15, pp. 183-193; 1977.

A review of experiments examining the carcinogenicity of

eosin and eosin disodium salt is presented. Wistar rats received po administrations of eosin, Saitama rats received sc injections of eosin disodium salt, and Wistar rats received sc injections of eosin; some tumors, especially mammary tumors, were noted. These data were insufficient for conclusive evaluation of carcinogenicity. No epidemiological studies on human exposure were available for study. (32 refs.)

77-6056 Copper 8-Hydroxyquinoline. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* (Lyon: International Agency for Research on Cancer): Vol. 15, pp. 103-110; 1977.

The animal data on the carcinogenicity of copper 8-hydroxyquinoline are reviewed. This compound was administered po and sc to male and female (C57BL/6 x CH3/Anf)F₁ and (C57BL/6 x ARK)F₁ mice. Reticulum cell sarcomas were observed only in male mice of the former strain. Since no human data were available, no evaluation of the carcinogenicity of this compound in humans is given. (15 refs.)

77-6057 Succinic Anhydride. (Eng.) IARC Working Group In: *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* (Lyon: International Agency for Research on Cancer): Vol 15, pp. 265-271; 1977.

The experimental data on the carcinogenicity of succinic anhydride are reviewed. Rats receiving sc injections of the compound developed sarcomas at the site of injection; however, the number of rats used in the experiment did not allow a thorough evaluation of carcinogenicity. Succinic anhydride was not mutagenic in *Salmonella typhimurium*. No human data were available for analysis. (20 refs.)

77-6058 The Metabolic Transformation of the Mycotoxin, Aflatoxin B₁. (Eng.) Steyn, P. S. (No affiliation given). *S Afr J Sci* 73(7): 200-201; 1977.

The various metabolic reactions that could be involved in the breakdown of aflatoxin B₁ are outlined, including conversion to aflatoxin M₁ and aflatoxicol H₁. (17 refs.)

7-6059 **Bladder Cancer and Saccharin.** (Eng.) Anonymous (No affiliation given). *Lancet* 2(8083): 12-593; 1977.

A recent Canadian study in which a positive association between bladder cancer and saccharin was noted in men is questioned. The results might not be valid for several reasons: no non-hormonal carcinogen is known to affect only one sex; adequate studies were performed on the coffee consumption and cigarette smoking habits of these patients; and controls may not have been properly selected. (19 refs.)

7-6060 **Teratogenic and Oncogenic Effect of Central Nervous System Medications.** (Fre.) Orgogozo, J. M. (Clinique neurologique, Centre Jean Abadie, 89, rue des Tablieries, 33077 Bordeaux Cedex, France); Loiseau, P. *Rev Prat* 27(35): 2225-2233; 1977.

A review of the teratogenic and oncogenic effects of CNS drugs revealed that the anticonvulsant diphenylhydantoin (DPH) is capable of inducing very rare and specific malformations, including craniofacial anomalies and finger malformations (typical hydantoin fetal syndrome). DPH is also believed to be oncogenic, and it may cause lymphomas associated with dysproteinemia and different immunological abnormalities. Leukemias, mainly the myeloblastic type, have also been attributed to DPH. Neuroblastoma was reported in two infants who presented with hydantoin fetal syndrome at birth. One died at 3 yr of age, but the other survived after an operation. Reference is also made to the development of malignant melanoma during L-dopa treatment in four patients, two of whom had known metastases. In addition, an exacerbation of bladder cancer has been attributed to patients treated with 5-hydroxytryptophan. (13 refs.)

7-6061 **Mechanisms in Inactivating Reactive Metabolic Products of Drugs.** (Ger.) Oesch, F. (Abt. Molekularpharmakologie, Pharmakologisches Institut der Universitat, Obere Zahlbacherstrasse 67, 6500 Mainz, W. Germany). *Arzneim Forsch* 27(9b): 1832-1835; 1977.

The relative contribution of epoxides metabolically produced from aromatic or olefinic drugs to the total mutagenicity of the reactive metabolites was evaluated. Epoxides were found to be responsible for most of the observed toxicity. They could be inactivated by epoxide hydratase, which controlled most tissue epoxide levels. (25 refs.)

77-6062 **Biochemistry of the Bacterial Catabolism of Aromatic Compounds in Anaerobic Environments.** (Eng.) Evans, W. C. (Dept. Biochemistry and Soil

Science, Univ. Coll. North Wales, Bangor, Gwynedd LL57 2UW, Wales). *Nature* 270(5632): 17-22; 1977.

The various natural pathways that exist for the microbial degradation of aromatic compounds are reviewed. The various topics discussed include catabolism of aromatic compounds, anaerobic photometabolism of benzoate by *Athiorhodaceae*, anaerobic metabolism of benzoate through "nitrate respiration", and methanogenic fermentation by a consortium adapted from rumen-liquor and/or sewage-digester sludge. Many of the more toxic chemicals, such as pesticides, are best degraded by a mixed adapted community of soil microorganisms than by a homogeneous population of organisms. Nevertheless, in some areas noxious chemicals may reach dangerous proportions and they require exceptional decontamination measures. (59 refs.)

77-6063 **Formation of Nitrosamines in the Digestive Tract.** (Fre.) Szyliet, O. (Laboratoire d'ecologie microbienne, I.N.R.A., 78350 Jouy-en-Josas, France); Ducluzeau, R.; Champ, M.; Klein, D. *Ann Nutr Aliment* 30(5-6): 805-812; 1976.

The recent literature on the toxic, mutagenic, and carcinogenic properties of nitrosamines is reviewed. In experiments using nitrates and nitrites at levels considerably higher than those found in a normal diet, nitrosamines have been shown to be formed in the digestive tract of animals. The role played by microflora in this *in vivo* synthesis is unclear, but *in vitro* experimental evidence supports this possibility. *In vitro* nitrosamine formation apparently depends on the type of amine and the pH of the medium. The ability of secondary amines to nitrosate increases with increased medium acidity. Bacteria can catalyze nitrosamine formation from precursor compounds, even at neutral pH. (32 refs.)

77-6064 **Vitamin C and Prevention of Nitrosamine Formation (Letter to Editor).** (Eng.) Weisburger, J. H. (Naylor Dana Inst., American Health Foundation, Valhalla, NY). *Lancet* 2(8038): 607; 1977.

A study of fish consumption in Japan indicated that formation of mutagenic nitrosamines and nitrosamides by treatment of fish with nitrite is prevented in the presence of ascorbate. This finding is in agreement with studies indicating that gastric cancer is lower in populations that consume high quantities of vitamin C. (16 refs.)

77-6065 **Quantitative Aspects of Human Exposure to Nitrosamines.** (Eng.) Archer, M. C. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology,

Cambridge, MA 02139); Wishnok, J. S. *Food Cosmet Toxicol* 15(3): 233-235; 1977.

The relative hazards of the various nitrosamines in food and the actual hazard posed by the ingestion of nitrosamine-contaminated food were evaluated. This analysis suggests that the potential hazard of environmental carcinogens should not be represented by simple concentration data. When animal data are being extrapolated to man, it should be kept in mind that carcinogens are more or less potent in humans. Also, low levels of highly active carcinogens may be more hazardous than much higher levels of less active carcinogens. It is concluded that if the threshold level for intracellular biochemical interactions (10^4 molecules/cell) computed for nitrosamines is relevant to carcinogenesis, these compounds found in food are not significantly hazardous. (20 refs.)

77-6066 Metabolism of Nitrates and Nitrites. (Fre.) Derache, R. (Groupe de recherches sur la toxicologie des aliments et des boissons, INSERM, U 87, 2, rue Francois-Magendie, 31400 Toulouse, France). *Ann Nutr Aliment* 30(5-6): 823-829; 1976.

The reactivity of nitrate and nitrite compounds in the digestive tract is discussed. Nitrate-nitrite compounds, once having entered the intestinal mucosa, may react with active biochemical groups. The chemical reactivity of nitrates-nitrites is discussed, along with their reduction by animal tissues. The high oxidation-reduction potential of nitrites may induce the oxidation of a large number of compounds (Fe^{+2} heme- Fe^{+3} hemin system; reduced cytochromes-oxidized cytochromes system, etc). The presence of nitrites in the blood may not be clearly established because of their high chemical reactivity. The transformation of nitrates into nitrites by a nitrate reductase in the tissues is possible. A discussion of nitrate excretion is presented. (25 refs.)

77-6067 Mutagenic Effects of Nitrates and Nitrites. (Fre.) Dorange, J. L. (I.N.R.A., Station de technologie des produits vegetaux, BV 1540, 21034 Dijon Cedex, France). *Ann Nutr Aliment* 30(5-6): 859-866; 1977.

Nitrates can be reduced to nitrites by various microflora. Thus, nitrates as well as nitrites must be considered as having mutagenic potential. Genetic toxicity is directly attributable to nitrites and their N-nitroso compounds, which are formed by the reaction of nitrites with secondary and tertiary amines, acid amines, or amides. Recent literature on the molecular mechanisms involved and on the genetic effects of these mutagens are analyzed. Assessment of the significance to man must be inferred from animal experiments because of the lack of epidemiologic data. (61 refs.)

77-6068 Stomach Cancer: Are Nitrites Responsible (Letter to Editor). (Fre) Delchier, J. C. (No affiliation given). *Nouv Presse Med* 6(21): 1815; 1977.

The incidence of stomach cancer is higher in regions where the drinking water has a high content of nitrites. A recent study of gastric fluids from 21 patients with duodenal ulcer, 12 with gastric ulcer, 6 with gastric cancer, and 30 controls indicated that levels of nitrite and bacterial nitrate reductase were significantly elevated in hypochlorhydric patients. (1 ref.)

77-6069 Carcinogenicity of N-Nitroso Compounds (Fre.) Montesano, R. (Centre international de recherche sur le cancer, 150, cours Albert-Thomas, 69372 Lyon Cedex 2, France). *Ann Nutr Aliment* 30(5-6): 867-874; 1976.

The toxic, mutagenic, and carcinogenic effects of N-nitroso compounds are analyzed. N-nitroso compounds (nitrosamines and nitrosamides) have been shown to be organ-specific: the kidney, respiratory system, esophagus, and liver are affected by nitrosamines, and the central and peripheral nervous systems, gastrointestinal system, and kidney are the principal target organs of nitrosamides. Esophageal tumors are encountered most frequently after treatment with N-nitrosamine-N-nitrosomethylalkylamines, but they are rarely observed following N-nitrosamide treatment. Embryotoxic, teratogenic, and carcinogenic effects of these compounds on rats, and the necessity of microsomal enzymes for the activation of nitrosamines (but not nitrosamides) are discussed. (24 refs.)

77-6070 Modification of Mucus in Animal Models of Disease. (Eng) Jones, R. (Dept. Experimental Pathology, Cardiothoracic Inst., Brompton Hosp., Fulham Road, London, SW3 6HP, England). *Adv Exp Med Biol* 89: 397-412; 1977.

Changes in the mucus secretion of goblet cells in animal models of airway disease, particularly those following tobacco exposure, are reviewed. Emphasis is placed on the number and types of goblet cells present. Although changes in the amount and type of glycoprotein are the earliest signs of irritation, they are also the earliest signs of tissue recovery. (32 refs.)

77-6071 Smoking and Cancer (2 Letters to Editor). (Eng) Miller, G. H. (Edinboro State Coll., Edinboro, PA); Schumaker, J. A.; Weiss, W. *JAMA* 238(19): 2015; 1977.

A re-evaluation of previous data implying an inverse relationship between the amount of smoking and the incidence of lung cancer in chloromethyl methyl ether workers indicated that this conclusion was based on erroneous categorization of smokers and non-smokers as well as unaccounted differences in exposure levels. However, this unusual association can still be justified as a valid and biologically important observation although the small numbers involved render the study statistically insignificant. (2 refs.)

77-6072 **Smoking and Cancer of the Uterine Cervix: Hypothesis.** (Eng.) Winkelstein, W. (Dept. Biomedical and Environmental Health Sciences, Sch. Public Health, Univ. California, Berkeley, CA 94720). *Am J Epidemiol* 106(4): 257-259; 1977.

Lung cancer and cancer of the uterine cervix are both squamous cell carcinomas, while squamous cell cancers of other organs are rare; thus the same etiological factor, cigarette smoking, may cause cancer at these two sites. Several studies are cited in which such a correlation was found, but more studies are needed to establish a definite risk of cervical cancer in smokers. (9 refs.)

77-6073 **Pathogenic Effects of Asbestos.** (Eng) Kannerstein, M. (Dept. Pathology, Barnert Memorial Hosp. Center, Paterson, NJ 07514); Churg, J.; McCaughey, W. T.; Selikoff, I. J. *Arch Pathol Lab Med* 101(12): 623-628; 1977.

The enormous increase in asbestos use during this century has necessitated the intensive study of its pathogenic effects. Exposure to asbestos leads to pulmonary parenchymal and pleural fibrosis and to increased incidences of pulmonary and gastrointestinal carcinoma and pleural and peritoneal mesothelioma. A relationship to laryngeal carcinoma is probable. Indirect occupational, domestic, and neighborhood exposure to asbestos has been associated with mesothelioma and possibly with pulmonary carcinoma. Low asbestos exposure has been shown to cause pulmonary fibrosis and pleural plaques. The physical characteristics of the asbestos fiber appear to be the principal factors in its carcinogenic action; the fine, short fibers, especially fragmented chrysotile, are able to reach the pleura, resulting in many of the pathogenetic and anatomical features characteristic of asbestos-related disease. (65 refs.)

77-6074 **Regarding Cyanophilic Bodies, Toxoplasma Cysts and Ferruginous Bodies (4 Letters to Editor).** (Eng.) Naylor, B. (Dept. Pathology, Univ. Michigan, Ann Arbor, MI 48104); Alvarez San Cristobal, A.; Takeda, M. *Acta Cytol (Baltimore)* 21(4): 490-492; 1977.

Whether or not the cyanophilic bodies found previously in the uterine cervix and vagina of a 59-yr-old woman are *Toxoplasma gondii* cysts is debated. The finding of ferruginous bodies in the sputum of a pulmonary blastoma patient is also discussed; asbestos may have played an etiological role in this case. (5 refs.)

77-6075 **The Dosimetry of ^{241}Pu Reconsidered.** (Eng) Poston, J. W. (Sch. Nuclear Engineering, Georgia Inst. Technology, Atlanta, GA 30332); Snyder, W. S.; Owen, L. W. *Health Phys* 33(3): 254-256; 1977.

The dosimetry on inhalation of class Y aerosol of pure ^{241}Pu is re-evaluated in terms of a beta emitter. With this model, the dose from the Pu and the daughter compound, ^{241}Am , to the lung, gastrointestinal tract, and bone could be reduced considerably. However, there was no sizeable reduction in the dose to the liver or gonads, the critical target organs. The results were the same for inhalation of class W or po ^{241}Pu . (9 refs.)

77-6076 **Toxicology of Selenium and Tellurium.** (Eng) Fishbein, L. (Natl. Center Toxicological Res., Jefferson, AR). In: *Advances in Modern Toxicology*. Goyer, R. A.; Mehlman, M. A., eds. (New York: John Wiley & Sons): Vol. 2, Toxicology of Trace Elements, 303 pp.; 191-240; 1977.

The toxicological, carcinogenic, teratogenic, and mutagenic aspects of selenium and tellurium are reviewed. In mammals, excess Se is teratogenic, hepatotoxic, and neurotoxic, retarding growth and causing muscular weakness. Se deficiency is associated with hepatic necrosis, retarded growth, muscular degeneration, and infertility. Neoplasia has not been found among the specific lesions attributed to Se deficiency in animals, and there has been no significant increase or decrease in cancer incidence among Se-exposed workers. Episodes of human toxicity from industrial exposure to Se compounds are rare. Although Te and its compounds possess low orders of acute toxicity, little is known regarding their chronic effects in low doses. The biological role of Te and its possible embryonic and cytogenetic effects require further exploration. (279 refs.)

77-6077 **Radium and Thyroid Cancer (Letter to Editor).** (Eng) Gerber, D. A. (State Univ. New York, Downstate Medical Center, Brooklyn, NY). *JAMA* 238(17): 1810; 1977.

When evaluating patients with previous head and neck irradiation for thyroid cancer, those who received intranaso-

pharyngeal radium or radon should be considered separately because of the much-reduced dose (3-8 R). This dose is less than that resulting from a ^{131}I scan. For comparison, in 1953, the dose to the thyroid from an esophagram was about 23 R. (5 refs.)

- 77-6078 Radiation-induced Chromosome Damage in Human Lymphocytes.** (Eng) Lloyd, D. C. (Natl. Radiological Protection Board, Harwell, Didcot, Oxon. OX11 0RQ, England); Dolphin, G. W. *Br J Ind Med* 34(4): 261-273; 1977.

The induction of chromosome aberrations in peripheral blood lymphocytes by ionizing radiation, along with techniques for their analysis, are reviewed, and dose-effect relationships for neutrons, x-rays, and cobalt-60 γ -radiation are presented. Problems in interpreting chromosome aberration yields in patients with known or suspected accidental overexposure to radiation include the effects of partial-body irradiation, the response to variations in dose rate, and the intermittent nature of some exposures. Two surveys of patients irradiated for medical purposes are described. In the first, lymphocyte aberrations were examined in rheumatoid arthritis patients receiving intra-articular injections of colloidal radiogold or radioyttrium. A proportion of the nuclide leaked from the joint into the regional lymphatic system. In the second survey, a comparison was made between the cytogenetic and physical estimates of whole-body dose in patients receiving iodine-131 for thyroid carcinoma. The two dose estimates were similar in patients who had received previous thyroid radioiodine ablation; the cytogenetic estimate of dose was considerably higher in patients with varying degrees of thyroid function. (9 refs.)

- 77-6079 Leukemia and Other Cancers Following Radiation Treatment of Pelvic Disease.** (Eng) Smith, P. G. (Dept. Health and Social Security, Cancer Epidemiology and Clinical Trials Unit, Oxford Univ., 9 Keble Road, Oxford, England). *Cancer* 39(4, Suppl): 1901-1905; 1977.

The incidence of leukemia in women receiving radiation treatment for cancer of the cervix was compared with that in women who were irradiated at lower doses for induction of an artificial menopause. The literature indicates that there is no significant increased risk of leukemia associated with radiotherapy for cervical cancer. However, women exposed to lower doses appear to show increased risks of both leukemia and cancer of the irradiated sites. Studies of women with benign gynecological disorders who had been treated with x-rays or radium revealed 33 cases of leukemia vs an expected 13.5. In addition, there were 352 cancers of the irradiated sites in these women vs 247.41 expected. Although these women could have had an increased susceptibility to cancer

because of the existing benign conditions, the results are more likely to reflect an inducing effect of the radiation. It is suggested that the higher dose given to cervical cancer patients is received by a small portion of the marrow, and it exerts a lethal effect. The lower and more uniformly distributed dose for benign conditions is less lethal to the marrow and may deliver a higher effective dose to the surviving cells, thus increasing the leukemia risk. (16 refs.)

- 77-6080 Radiation-associated Head and Neck Tumors.** (Eng) Southwick, H. W. (Dept. General Surgery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL 60612). *Am J Surg* 134(4): 438-443; 1977.

Head and neck tumors that frequently develop following exposure to ionizing radiation for benign conditions are reported. Skin cancers have occurred in patients irradiated for hirsutism, acne, and capillary hemangiomas, and mucosal tumors have occurred after radiation treatment for thyrotoxicosis. However, the thyroid, parathyroid, and salivary glands seem particularly susceptible to the development of neoplasms following irradiation. Even relatively small doses of ionizing radiation carry a long-term potential carcinogenic risk. (62 refs.)

- 77-6081 Radiation Risks.** (Eng) McGinty, L. (No affiliation given). *New Sci* 76(1076): 268; 1977.

Reports of cancer incidence in workers exposed to radiation at a nuclear power facility may be incomplete since follow-up studies on employees who have left the plant were not included. However, health hazards in the nuclear industry are not being overlooked; rather, a registry of radiation workers will provide data in the future. (no refs.)

- 77-6082 Symposium on the Radiobiological Response Relationships at Low Doses. The Effects of Small Doses of Ionizing Radiation. Fundamental Biophysical Characteristics.** (Eng.) Rossi, H. H. (Radiological Res. Lab., Columbia Univ., Coll. Physicians and Surgeons, New York, NY 10032). *Radiat Res* 71(1): 1-8; 1977.

Microdensitometric considerations suggest that the first step in radiation-induced carcinogenesis is the induction of a subcellular lesion; it also follows that the direct effect of ionizing radiation on individual cells is proportional to the dose. The biological effect is probably due to a single charged particle. For low linear energy transmission (LET) radiation and neutrons having energies of the order of a few hundred kiloelectron volts, this probability differs by a factor of 10 to > 100. Relative biological effectiveness declines at intermediate

doses because of the quadratic increase in LET radiation. An application of these findings to the incidence of leukemia in Japan following the atomic radiation exposure revealed that the maximal permissible neutron dose should be reduced. (16 refs.)

- 77-6083 **The Shape of the Dose-Response Curve for Radiation Carcinogenesis. Extrapolation to Low Doses.** (Eng.) Brown, J. M. (Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA 94305). *Radiat Res* 71(1): 34-50; 1977.

Extrapolation to low doses of the radiation dose-response curves for radiation carcinogenesis is presented based on high linear energy transmission (LET) data. Since the lower portion of the latter curve is linear and without a threshold dose, the shape of the curve following low LET radiation must be likewise. Based on high LET data, the induction of cancers by radiation should follow the equation $I = C + \alpha D + \beta D^2$, with I , the incidence at dose D ; C , the control incidence at dose 0; and α and β as constants. The values for α and β extend over a wide range, but a relation between DNA content/genome and the value of α/β was identified. Thus the larger the α/β ratio, the smaller the volume in which two radiation-induced lesions may interact to produce a larger lesion. The dose-response curve following low LET radiation is linear up to a dose of approx 100 rads. The max value of the "protraction factor" (by which risk estimates from large acute doses are divided to obtain risk at protracted lower exposures) will be 2.0 if these risk estimates have been derived from doses of approx 100 rads. A comparison of the rate of cancer induction by high and low LET irradiation for thyroid carcinoma, leukemia and breast cancer in humans suggests a higher risk/rad at low doses than at high ones. (66 refs.)

- 77-6084 **Cancer Induction by Low-Level Radiation Doses.** (Ger.) Fuchs, G. (Internationales Institut für den Frieden, Mollwaldplatz 5, A-1040 Vienna, Austria). *Radiobiol Radiother (Berl)* 18(2): 151-155; 1977.

Review of the current literature on the induction of cancer by low-level radiation led to the conclusion that the doses in use are not carcinogenic or leukemogenic. Recent studies by the National Research Council and by other individuals are criticized because they extrapolate the incidence tumors induced by whole-body irradiation onto a whole population. In clinics, fractionated doses are used. From 1946 to 1974, there were no radiation-induced malignancies in 488 patients with breast carcinoma who received a total of 6,800 rads in fractionated doses. According to the literature, 10-20 patients should have developed a tumor. Overall, no cases of radiation-induced neoplasia or leukemia developed in a total of 2,000 patients with various cancers given low level radiation treatment. (10 refs.)

- 77-6085 **Viral Carcinogenesis and Reverse Transcription.** (Spa) Valladares, Y. (Departamento de Biología y Bioquímica del Cáncer, Consejo Superior de Investigaciones Científicas, Madrid, Spain). *Rev Esp Oncol* 23(2): 293-325; 1976.

The state of the art of studies on viral carcinogenesis and the role of reverse transcriptase in this process is presented. The biochemical and molecular processes involved in the neoplastic transformation of cells by viruses are described. (111 refs.)

- 77-6086 **Biochemical and Molecular-biological Study of Tumors and Processes of Carcinogenesis.** (Rus) Seits, I. F. (No affiliation given). *Vopr Onkol* 23(9): 20-24; 1977.

The emphasis of research on viral carcinogenesis has shifted from the search for oncogenic viruses in humans to the attempt to isolate a "cancer gene" carried by viruses. The mechanism by which individual genes are suppressed requires further study. (no refs.)

- 77-6087 **Etiology of Bovine Leukemia.** (Rus.) Laktionov, A. M. (VGNKI, USSR); Kozyrev, Iu. A.; Alekhin, R. M. *Veterinariia* (6): 52-56; 1977.

The bovine leukemia virus detected in the lymphocytes from leukemic cattle is thought to carry group-specific and type-specific antigens. The frequency of leukemia is somewhat higher in inbred animals, indicating a possible role for hereditary factors in the etiology of the disease. (no refs.)

- 77-6088 **Oncogenicity of Herpes Simplex Virus and Lupidon.** (Ger.) Petersen, E. E. (Klin. d. Albert-Ludwig-Univ., Zentrum für Hygiene, Abt. Virologie, Hermann-Herder-Strasse 11, 7800 Freiburg/Breisgau, W. Germany). *Z Hautkr* 52(7): 417-426; 1977.

The role of herpes simplex virus type 2 (HSV-2) in the development of cervical carcinoma is discussed. Although women with this cancer have a higher than normal percentage of antibodies against HSV-2, molecular-virological examinations have not confirmed the presence of the virus in the tumor cells. Similarly, viral DNA has not been demonstrated in hamster embryo cells transformed by UV-inactivated HSV-2; these cells induce fibrosarcomas when injected into newborn hamsters. Lupidon, which contains heat-inactivated HSV-2, was not oncogenic when tested in vitro and in vivo in newborn hamsters. (4 refs.)

- 77-6089 **Relation of Herpes Simplex Virus to Human Malignancies.** (Eng) Rawls, W. E. (Dept. Pathology, McMaster Univ., Hamilton, Ontario, Canada); Bacchetti, S.; Graham, F. L. *Curr Top Microbiol Immunol* 77: 71-95; 1977.

The relationship between herpes simplex virus type 2 (HSV 2) and squamous cell carcinoma of the cervix is reviewed. The bulk of the evidence for an association comes from epidemiologic and seroepidemiologic studies in which patients with cervical cancer, or at risk of disease, either have evidence of HSV 2 infections or possess antibodies to HSV 2. However, viral sequences have yet to be detected in cervical carcinoma cells; more sensitive techniques are currently being developed. Transformation of cultured cells by HSV DNA has already been demonstrated, but little information is available on the in vivo carcinogenicity of HSV, and there is no known similar virus producing similar neoplasms in animals. The data on HSV 2 is compared to that on the association between Epstein-Barr virus and African Burkitt's lymphoma and nasopharyngeal carcinoma. If there is a link between HSV 2 and cervical cancer, the development of a vaccine could lower the incidence, as could a change in sexual habits. (129 refs.)

- 77-6090 **Morphogenic Studies of Herpesvirus and Oncornavirus from Leukemic and Normal Guinea Pigs.** (Eng.) Fong, C. K. (Virology Lab., Veterans Admin. Hosp., West Haven, CT 06516); Hsiung, G. D. *Fed Proc* 36(9): 2320-2327; 1977.

Ultrastructural studies of the development of the guinea pig herpeslike virus (GPHL virus) in cultured cells revealed the presence of viral nucleocapsids [90-100 nanometers (nm) diameter] in the nucleus, virus particles budding from the inner nuclear membrane and budding into nuclear vacuoles, and enveloped virus particles in the nuclear vacuoles. Intracellular non-virus-containing inclusions and filamentous structures were also observed. Naked viral nucleocapsids were frequently seen in the cytoplasm during later stages of GPHL virus infection either in close association with or budding into the cytoplasmic vacuoles. Budding at the cell surface was seen in a few instances. Enveloped virus particles were commonly found in cytoplasmic vacuoles and in the extracellular space. Ultrastructural studies of guinea pig oncornavirus (GPO) in guinea pigs with L₂C leukemia showed two morphologically distinct oncornavirus particles: 90 to 100 nm intracisternal A-type virus particles with electron-lucent centers and 90 to 110 nm extracellular mature virus-like particles with electron-dense cores. Cultured guinea pig cells treated with bromodeoxyuridine showed 90 to 100 nm intracytoplasmic A-type virus particles with electron-lucent centers and 110 to 120 nm extracellular 'mature' virus particles with dense cores. (38 refs.)

- 77-6091 **Virological Studies of Guinea Pig Leukemia: An Overview with Reference to Herpesvirus and Oncornavirus.** (Eng.) Hsiung, G. D. (Virology Lab., Veterans Admin. Hosp., West Haven, CT 06516). *Fed Proc* 36(9):2285-2289; 1977.

Both a guinea pig oncornavirus (GPO virus) and a guinea pig herpeslike virus (GPHL virus or Caviid herpesvirus 2) have been identified in tissues and cells derived and cultured from L₂C leukemic guinea pigs. GPHL virus can be isolated from the WBC of leukemic and normal guinea pigs, and it can transform hamster embryo cells in culture. GPO virus, although seldom evident in normal adult guinea pig tissues, has been occasionally observed in placental cells or in the gonads of both male and female fetuses. It can be induced by 5-bromo-2'-deoxyuridine in all primary cultured cells derived from normal guinea pigs. Superinfection of guinea pigs with infectious herpesvirus in the presence of the endogenous oncornavirus led to the development of self-limited lymphoproliferative changes characterized by hyperplasia in the spleen and lymph nodes that persisted for up to 12 mo. Inoculation of guinea pigs with oncornavirus alone, however, caused a significantly lower incidence of hyperplasia, suggesting that there was an interaction between the GPHL virus and the GPO virus. These findings are discussed in relation to the association of herpesvirus and/or oncornavirus with tumors in man and animals. (38 refs.)

- 77-6092 **Immunological Studies of the Guinea Pig L₂C Leukemia.** (Eng.) Green, I. (Lab. Immunology, Natl. Inst. Allergy and Infectious Disease, NIH, Bethesda, MD 20014); Forni, G.; Konen, T.; Hu, C. P.; Schwartz, B. D.; Kask, A.; Shevach, E. M. *Fed Proc* 36(9): 2264-2267; 1977.

The guinea pig leukemic BZ-L₂C cell subline not only lacks Ia antigens, it also lacks a tumor-specific transplantation antigen (TSTA), as measured by immunization protection tests. The other four sublines of L₂C have a TSTA. Although preimmunization of strain 2 guinea pigs with BL-L₂C afforded no protection against challenge with an Ia+ leukemia, strain 2 animals preimmunized with an Ia+ line of the leukemia were protected against a subsequent challenge with both Ia+ and Ia- lines of BZ-L₂C. This demonstrated that the BZ-L₂C line did not lack a TSTA, but rather the TSTA was not immunogenic when on the BZ-L₂C cell. The TSTA on the BZ-L₂C cell, however, can be recognized and destroyed by an animal previously immunized with an L₂C cell bearing both TSTA and Ia antigens. Possible explanations for this situation were discussed. TSTA was solubilized with KCl from either an Ia+ or an Ia- BZ-L₂C, and immunization by either extract appeared to be equally protective. The possibility that the TSTA may be the idiotype IgM already identified on the surface of all five L₂C variants was considered. (32 refs.)

77-6093 **Overview of the Structure and Function of the Major Histocompatibility Complex of the Guinea Pig.** (Eng.) Shevach, E. M. (Lab. Immunology, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD 20014); Schwartz, B. D. *Fed Proc* 36(9): 2260-2263; 1977.

An overview of the structure and function of the major histocompatibility complex (MHC) of the guinea pig (GPLA complex) is presented. Homologous with murine H-2D and K and human HLA A and B antigens, the guinea pig possesses S and B (B.1, B.2, B.3, and B.4) antigens, in both lymphoid and non-lymphoid tissues. Cross-immunization of inbred strain 2 and strain 13 guinea pigs identified immune response (Ir) genes that controlled response to the 2,4-dinitrophenyl derivative of a copolymer of L-glutamic acid and L-lysine (DNP-GL) by strain 2 and response to a copolymer of L-glutamic acid and L-tyrosine (GT) by strain 13. Further studies delineated other antigenic determinants controlled by the I region (guinea pig equivalent of the I region of murine MHC) designated Ia 1, 2, 3, 4, 5, 6, and 7 and detected only in lymphoid tissues. Strain 2 and 13 animals were found to be both B.1 and S positive and to differ only in the I-region. A genetic map of the I region of the GPLA complexes of strain 2 and strain 13 guinea pigs was prepared and arranged according to structural homology. These considerations should be important for studies of tumor transplant immunology, including the transplantation genetics of various L₂C leukemic sublines. (19 refs.)

77-6094 **HLA and Association with Malignancy: A Critical View.** (Eng) Dausset, J. (Centre Hayem, Hosp. St. Louis, Paris, France). *Prog Clin Biol Res* 16: 131-144; 1977.

The association of the major histocompatibility locus antigen (HLA) with malignancy was reviewed critically. Associations between the incompatibility locus and nonmalignant diseases due to the presence in the HLA complex of a susceptibility gene for the disease, in linkage-disequilibrium with some HLA markers (eg, multiple sclerosis with B7, or with DW2), are generally accepted. However, for malignant disease these associations are very rare (nasopharyngeal carcinoma is the only example) or much weaker. Possible reasons for this observation were offered: (1) there could be a lesser linkage-disequilibrium between a malignancy susceptibility gene and the HLA markers; (2) a gene for susceptibility to malignancy might be in linkage with the HLA complex without any linkage-disequilibrium; (3) a recessive gene for susceptibility may be present in the HLA complex; and, finally, (4) genetic control of resistance to disease progression may be associated with the HLAs. Methodology for detecting these associations is described. Possible associations between A2 and acute lymphocytic leukemia, A1 and B8 and leukemia, B8 and intestinal malignancies, and BW35 and rectal malignancy are also discussed. (31 refs.)

77-6095 **Association of Histocompatibility HLA Antigens with Malignant Disease.** (Pol) Turowski, G. (Pracownia Immunologii Transplantologicznej, III. Klin. Chir. AM, 31-531 Krakow, ul. Grzegorzeczka 16, Poland); Pietrzyk, J. J. *Patol Pol* 28(1): 17-27; 1977.

A review of the literature data shows a significantly increased incidence of histocompatibility antigens in patients with Hodgkin's disease, leukemia and other malignant neoplasms as compared with controls. The findings suggest a genetic predisposition to these diseases. The role of the immune system in the development of malignancy is considered. (42 refs.)

77-6096 **Function of the Immune Genes.** (Eng) Jones, L. (Genetics Lab., Oxford Univ., Oxford, England); Barnstable, C. *New Sci* 76(1076): 280-282; 1977.

A review is presented of data on different functions of the immune gene complex. An evolutionary tree indicates that all populations may have diverged from a common ancestor. The only link between HLA and cancer is the A2-nasopharyngeal carcinoma association, although peculiar Ia antigens may exist in patients with chronic lymphocytic leukemia. It is possible that the genes of the HLA region control tissue-specific interactions that assure correct tissue adhesiveness. (1 ref.)

77-6097 **Cellular and Genetic Bases for Modifications of Tolerance Inducibility as a Function of Age.** (Fre.) Cinader, B. (Inst. Immunology, Dept. Medical Genetics, Medical Sciences Building, Room 4366, Univ. Toronto, Toronto, Ontario, Canada M5S 1A8). *Ann Immunol (Paris)* 128 C(1/2): 415-425; 1977.

Continuous alteration of the immune response as a function of cytodifferentiation is examined. Tolerance inducibility was used to detect aging processes with respect to progressive changes in T-cell subpopulations. Studies were initiated on mice shown to be resistant to tolerance induction by rabbit γ -globulins. Accessory cells (defined experimentally by their resistance to radiation and adherence to glass) were found to be implicated in resistance to tolerance in thyroidectomized and nonthyroidectomized mice. The results indicate that the resistance to tolerance inducibility involves changes related to aging in T-cell subpopulations and that this change is manifested by an interaction with accessory cells. (24 refs.)

77-6098 **Immunology of Atrophic Gastritis.** (Eng.) Glass, G. B. (Dept. Medicine, New York Medical Coll., Fifth Ave. at 106th St., New York, NY 10029). *NY State J Med* 77(11): 1697-1706; 1977.

Chronic atrophic gastritis usually begins as a superficial gastritis leading to infiltration of the gastric mucosa. If autoimmune mechanisms do not arrest the process, gastric atrophy and the associated metaplasia will usually develop. The formation of immune complexes in the serum of patients with atrophic gastritis is discussed. (60 refs.)

- 77-6099 **Significance of Immunological Defects for Carcinogenesis.** (Ger.) Warnatz, H. (Institut für Klinische Immunologie der Universität, Postfach 3560, D-8520 Erlangen, W. Germany). *Internist (Berlin)* 18(5): 264-268; 1977.

Studies of the relationships between immunological defects and neoplasms are reviewed. Tumor antigens were detected in experimental tumors induced by methylcholanthrene and viruses. Fetal antigens (α_1 -fetoprotein and carcinoembryonic antigen) were found frequently in patients with malignant tumors. Recent findings suggest that these antigens have a suppressive effect on cellular immunity. Chemical carcinogens and oncogenic viruses were also found to suppress humoral and cellular immunity. A significant increased tumor incidence was found in patients with immune deficiency syndromes (Louis-Barr syndrome, Wiskott-Aldrich syndrome, Chediak-Higashi syndrome, acquired agammaglobulinemia, and dysgammaglobulinemia), which indicates that inborn or acquired immune deficiency can be associated with increased tumor incidence. Primary and secondary defects of the immune defense system, the induction of suppressor T cells, certain genetic factors (H2 genes and HLA B5 antigens), enhancement by blocking serum factors, and shedding or antigen modulation help the tumor escape immunosurveillance. Recent findings suggest that the immune response and carcinogenesis are interrelated. (47 refs.)

- 77-6100 **The Interaction of Chemical Carcinogens and the Immune Response.** (Eng) Thor, D. E. (Dept. Microbiology, Univ. Texas Health Science Center at San Antonio, San Antonio, TX 78284); Reichert, D. F.; Flippen, J. H. *J Reticuloendothel Soc* 22(3): 243-252; 1977.

The relationship between immunosuppression and chemical carcinogenesis is reviewed. Particular attention is placed on macrophage metabolism, complement synthesis, humoral antibody synthesis, and both contact sensitivity of lymphocytes and suppression of T cells by chemical carcinogens. (71 refs.)

- 77-6101 **Genetic and Environmental Interactions.** (Eng) Strong, L. C. (Section Medical Genetics, Univ. Texas System Cancer Center, M. D. Anderson Hospital and

Tumor Inst., Houston, TX 77030). *Cancer [Suppl]* 40(4): 1861-1866; 1977.

Cancer may result from a multistage process occurring over a long period of time. Initial and progressive stages of carcinogenesis may be modified by both genetic and environmental factors. Theoretically, genetic factors may alter susceptibility to the carcinogenic effects of an environmental agent at the initial exposure due to variation in metabolism of the carcinogen or variation in specific target cell response to the active carcinogen, or during the latent phase due to numerous factors that might increase the probability of tumor expression, including growth-promoting factors or immunodeficiency states. Observed genetic and environmental interactions in carcinogenesis include an association between genetically determined inducibility of aryl hydrocarbon hydroxylase and smoking-related cancers, familial susceptibility to certain environmental carcinogens, an association between hereditary disorders of mutagenesis and carcinogenesis, and enhancement of tissue-specific, dominantly inherited tumor predisposition by radiation. Multiple primary tumors occur frequently in genetically predisposed individuals. Specific markers for susceptibility must be sought in order that high-risk individuals be identified and appropriate measures taken for early cancer detection or prevention. (82 refs.)

- 77-6102 **Endogenous Factors in the Development of Cancer.** (Rus) Neiman, I. M. (Inst. Nutrition, Acad. Medical Sciences USSR, Moscow, USSR); Andrianova, M. M.; Kozlova, I. N.; Finogenova, M. A. *Patol Fiziol Eksp Ter* (5): 51-55; 1977.

Current views on endogenous factors in the development of cancer are reviewed. The considerable differences in cancer susceptibility show that genetic predisposition plays a major role in this process. Exogenous carcinogenic factors act only as potent accelerators of malignant transformation. Cells susceptible to malignant transformation contain a provirus with normal physiological functions that can be easily transformed into a carcinogenic virus by exogenous carcinogens. Spontaneous transformation would take a very long time. Endogenous synthesis of a specific substrate of malignancy is controlled by the endocrine, nervous, and, especially, immunocompetent systems. Malignant transformation is preceded by immunosuppression, which is enhanced further by ongoing tumor growth. (23 refs.)

- 77-6103 **Origin of Reed-Sternberg Cells (Letter to Editor).** (Eng.) Bacigalupo, A. (Dept. Hematology and Clinical Immunology, Ospedale Regionale S. Martino, Genoa, Italy); Santini, G.; Piaggio, G.; Marmont, A. M. *Lancet* 2(8038): 608-609; 1977.

Antilymphocytic globulins have been found to discriminate between cytochemically proven lymphoid, myeloid and monocytic cell lines. Myeloid-absorbed antilymphocytic globulins also interact with Reed-Sternberg cells. It is suggested that these globulins recognize an antigenic complex expressed while mature T and B cell markers are lacking. (8 refs.)

- 77-6104 **Present Concepts on Origin of Human Leukemia.** (Cze) Libansky, J. (Ustav hematologie a krevni transfuze, Prague 2, U nemocnice 1, Czechoslovakia). *Vnitř Lek* 23(8): 794-801; 1977.

Ionizing radiation and chemical substances (especially benzene) are the principal known etiological factors in human leukemia. Type C RNA viruses are also believed to be involved. Susceptibility to leukemia shows broad individual variation, suggesting the involvement of genetic determinants. (34 refs.)

- 77-6105 **Preleukemia. Cytogenetic Clues in Some Confusing Disorders.** (Eng) Nowell, P. C. (Dept. Pathology, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA 19104). *Am J Pathol* 89(2): 459-476; 1977.

Cytopenia, myeloproliferative disorders and certain congenital and childhood disorders that increase the patient's risk of developing leukemia may be defined as preleukemia or preclinical leukemia. It is suggested that these disorders are characterized by a clone of cells with selective growth advantage, differing from leukemia only in degree. Genetic control of this clone is discussed. (38 refs.)

- 77-6106 **Chromosomal Factors in Leukemogenesis.** (Fre) Engel, E. (Sch. Medicine, Vanderbilt Univ., Nashville, TN 37232). *Schweiz Med Wochenschr* 107(41): 1426-1436; 1977.

The major chromosomal abnormalities observed during animal and human leukemogenesis are reviewed. The cytogenetic abnormalities identified to date in both the myeloproliferative and lymphoproliferative disorders are discussed. (84 refs.)

- 77-6107 **Chromosomes and Cancer.** (Eng) Levan, A. (Inst. Genetics, Univ. Lund, S-223 62 Lund, Sweden); Levan, G.; Mitelman, F. *Hereditas* 86(1): 15-29; 1977.

The development of modern cancer cytogenetics is reviewed. The Philadelphia chromosome of chronic myelogenous leukemia (CML), discovered in 1960, was unique in showing a strict correlation between specific chromosomal deviation and malignant disease. Detailed chromosome analysis of large series of experimental tumors established the distinction between significant and accidental chromosome deviations and demonstrated that the former were nonrandom and formed predetermined patterns. They were correlated with the inducing agent, rather than the tissue type from which the tumor developed. Systematic analysis of chromosome aberrations in > 600 human neoplasms comprising 12 tumor types showed that most chromosomes were unaffected, the significant deviations being limited to 10/24 human chromosomes. It was suggested that genes of special importance to malignant development are located in a few specific chromosomes. The cancer-associated phenomena of homogeneously staining chromosome regions and double minute chromosomes are briefly described, and a tentative interpretation is proposed. (10 refs.)

- 77-6108 **Theories of Quasi-linkage and 'Affinity': Some Implications for Population Structure.** (Eng.) Mike, V. (Biostatistics Lab., Memorial Sloan-Kettering Cancer Center, New York, NY 10021). *Proc Natl Acad Sci USA* 74(8): 3513-3517; 1977.

Theories of quasi-linkage, the nonrandom assortment of genes located on different chromosomes, are reviewed, and the relationship of this phenomenon to the inheritance of susceptibility to cancer and other diseases is discussed. There are two general theories to explain quasi-linkage: (1) variable meiotic affinity, in which the association of one allele with another would follow the parental pattern; and (2) sustained meiotic affinity. The question of whether sustained meiotic affinity can influence population structure in a manner unattainable by other known modes of heredity was examined mathematically. For a two-locus, two-allele system, equilibrium is attained with the gametic phase disequilibrium $D > 0$, leading to a permanent excess of the preferred genotypes. The three genes for which quasi-linkage has been observed all have a connection with leukemia virus in mice. Each of these loci, Gv-1, H-2, and Fv-1, can be suspected of affecting the susceptibility of individual mice to leukemia and other cancers of similar viral etiology. If groups of unlinked alleles predispose to disease syndromes, a mechanism for preserving certain constellations of alleles and eliminating others has selective advantage. Sustained affinity guarantees a permanent excess of the favorable genotypes. Although the effect may be small in any one instance, quasi-linkage, as reported in the literature, is common, so that multiple effects may be operative. (12 refs.)

- 77-6109 **The Development of Carcinoma of the Colon.** (Eng.) Waye, J. D. (Dept. Medicine, Mount

Sinai Sch. Medicine, City Univ. New York, New York, NY). *Am J Gastroenterol* 67(5): 427-429; 1977.

It is suggested that colonic polyps lead to cancer of the colon. Most polyps remain in Stage 0 for the lifetime of the patient, but some may develop a small focus of carcinoma at the tip. Villous tumors have a higher rate of malignant change than adenomatous polyps. (15 refs.)

- 77-6110 **Malignant Transformation of Gastric Ulcer: Changes in Thinking.** (Jpn.) Murakami, T. (Tokyo Medical Dental Coll., 1-5-45 Yushima, Bunkyo-ku, Tokyo 113, Japan). *Stomach Intest* 11(5): 561-564; 1976.

Hauser's hypothesis on the malignant transformation of gastric ulcers is examined in view of recent clinical findings. The malignant cycle is stated to proceed as follows: (1) ulceration; (2) fibrosis; (3) fibrotic cancer; (4) Hauser's ulcerated cancer, seemingly cured by appearance of regenerated benign epithelium; (5) new fibrotic cancer; (6) Hauser's ulcerated cancer due to recurrence of ulcer. However, Hauser's ulcerated cancer could also be due to ulceration of a mucosal cancer. Long-term clinical studies (20-30 yr) seem necessary to ascertain the validity of Hauser's hypothesis. (17 refs.)

- 77- **Considerations on the Preneoplastic Lesions of the Mammary Gland.** (Eng) Gullino, P. M. (Lab. Pathophysiology, NCI, Building 10, Room 5B36, NIH, Bethesda, MD 20014). *Am J Pathol* 89(2): 413-430; 1977.

The induction and the subsequent malignant transformation of preneoplastic mammary lesions are discussed based on current experimental work. Carcinogenic agents include chemicals and viruses. Transplantation of hyperplastic outgrowths, evaluation of growth potential, and the relationship between preneoplasia and tumor dormancy are considered. (100 refs.)

- 77-6112 **Prostate Carcinogenesis in the AXC Rat.** (Eng.) Shain, S. A. (Southwest Foundation Res. and Education, 8848 W. Commerce St., San Antonio, TX 78284); McCullough, B.; Nitchuk, M.; Boesel, R. W. *Oncology* 34(3): 114-122; 1977.

The ventral prostate of the senescent rat has a decrease in cytoplasmic and nuclear androgen receptor content, diminished capacity to synthesize 5 α -dihydrotestosterone (5 α -DHT), and an increased capacity to synthesize Δ^4 -androstenedione (Δ^4 -AD). The decrease in cytoplasmic androgen receptor is related to a diminished dependence on androgen for ventral prostate cell number. The dorsolateral prostate of the aging rat, however, does not contain demonstrable cytoplasmic androgen receptor and the nuclear recep-

tor content per cell is 20% of that of the ventral prostate. Its 5 α -DHT synthesis capacity is twice as great as that of the ventral prostate and its Δ^4 -AD synthetic capacity is 35% of that shown by the ventral prostate. The ventral prostate (but not the dorsolateral prostate) develops spontaneous adenocarcinomas at a frequency of 70% in aged (30-46 mo old) virgin male AXC rats. These tumors are transplantable to isogenic hosts to yield transplantable adenocarcinomas whose morphologic features are very similar to the primary neoplasms. Testosterone metabolism by spontaneous and transplantable ventral prostate adenocarcinoma demonstrates increased Δ^4 -AD synthesis and diminished 5 α -DHT synthesis relative to the lesion-free ventral prostate of senescent AXC rats. The data indicate that aging-associated changes in androgen metabolism and regulation of cell number in the ventral prostate may be related to the development of prostate adenocarcinoma and that the rat represents an appropriate model for the study of prostate carcinogenesis. (42 refs.)

- 77-6113 **The Role of the Pathologist in Environmental Medicine and Public Health: A Review.** (Eng.) Higginson, J. (International Agency Res. Cancer, 150 Cours Albert Thomas, 69372 Lyon, France). *Am J Pathol* 86(2): 460-484; 1977.

The role of the morbid anatomist and clinical pathologist in environmental carcinogenesis is summarized. In the past, the pathologist has contributed considerably to the identification of rare tumors and their etiology. He has an important role to play in the future in providing more accurate data on which epidemiology studies can be developed. Modern pathologists should have an understanding of toxicologic and pharmacologic techniques and their potential application to biologic material so that they can correlate and develop multidisciplinary approaches to the identification of environmental hazards. Some of these approaches are illustrated and their potential developments outlined. (105 refs.)

- 77-6114 **The Importance of Environmental Factors in Human Cancer: The Role of Epidemiology.** (Fre) Higginson, J. (Centre International de Recherche sur le Cancer, 150, Cours Albert-Thomas, F69372 Lyon Cedex 2, France); Muir, C. S. *Bull Cancer (Paris)* 64(3): 365-384; 1977.

It is suspected that over 80% of all human cancers are of environmental origin; data supporting this assertion are reviewed. Examples of environmental agents that are carcinogenic are given. Mortality data by site and geographical location are presented. (58 refs.)

- 77-6115 **Some Epidemiologic Observations on Cancer of the Female Breast.** (Eng.) Cutler, S. J. (Div. Biostatistics and Epidemiology, Dept. Community Medicine and International Health, Georgetown Univ. Sch. Medicine, Washington, DC 20007). *Int J Radiat Oncol Biol Phys* 2(7-8): 753-754; 1977.

Two-thirds of all cancers in American women occur in five organ sites: breast (27.2%), large intestine (15.1%), uterus (14.4%), lung (5.3%), and ovary (5.1%). Breast cancer accounts for one-third of all cancers in women between the ages 40 and 70. Variation in the age incidence pattern in different parts of the world suggests that the factors associated with breast cancer development in premenopausal and postmenopausal women are different, eg, ovary-related in younger women and adrenal-related in older women. Other observed variations include higher incidences among economically more affluent women, among female relatives of breast cancer patients, among nulliparous women, and among women whose first child was born relatively late in life. These observations suggest that the development of breast cancer is influenced by genetic factors, such as endocrine levels, as well as behavioral and environmental factors. (7 refs.)

- 77-6116 **The Epidemiology of Breast Cancer.** (Eng.) Levin, M. L. (Johns Hopkins Hosp., Baltimore, MD 21205); Thomas, D. B. *Prog Clin Biol Res* 12: 9-35; 1977.

In this review, the major factors known or suspected to increase the risk of developing breast cancer in women are discussed. These risk factors include increasing age, age > 30 at birth of first child, nulliparity, menarche before 13 yr, natural menopause after 50 yr, oophorectomy after age 45, obesity, exposure to ionizing radiation, previous cancer of the breast, endometrium, colon-rectum, salivary gland, and/or ovary, family history of breast cancer, and fibrocystic breast disease (especially with ductal atypia). Treatment of hypertension with reserpine has also been reported to increase the risk of breast cancer. In addition, studies of male breast cancer have implicated hormones in the genesis of the disease, as well as familial tendencies. (80 refs.)

- 77-6117 **Epidemiological Aspects of Breast Cancer in Women. Part I.** (Ita.) Petrella, G. (II Facolta di Medicina e Chirurgia, Universita di Napoli, Naples, Italy); De Ianni, L.; Mozzillo, N.; Bucci, L.; Gallipoli, A. *Rass Int Clin Ter* 57(8): 503-507; 1977.

The general risk factors of breast cancer, including ethnic-geographic distribution (the incidence of breast carcinoma in Japanese women living in the U.S. is 50% greater than that in their counterparts in Japan), age (breast cancer occurs most frequently before and after menopause), and absence of

lactation (breast cancer is more prominent in women who have not breastfed their babies). (no refs.)

- 77-6118 **Epidemiological Aspects of Breast Cancer in Women. Part II.** (Ita.) Petrella, G. (II Facolta di Medicina e Chirurgia, Universita di Napoli, Naples, Italy); De Ianni, L.; Mozzillo, N.; Gallipoli, A.; Musella, S. *Rass Int Clin Ter* 57(8): 508-513; 1977.

Concerning the epidemiology of breast cancer in women, general risk factors are stated to include an individual's hormonal picture (greater breast cancer incidence in women with decreased excretion of ethylcholanone and in women with alterations in the estriol-estrone-estradiol equilibrium), obesity, and change in size of the X chromosome. Family precedent and cystic mastopathy are among the specific risk factors. (34 refs.)

- 77-6119 **Reproductive Function and Breast Carcinoma.** (Rus.) Levshin, V. F. (Dept. Epidemiology Malignant Tumors, Oncological Scientific Center, Moscow, USSR). *Vopr Onkol* 23(6): 86-95; 1975.

Highly conflicting data on the role of reproductive function in the etiology of breast carcinoma are reviewed. It is recommended that analysis of factors such as age, sexual activity, childbirth, breast-feeding, abortions and miscarriages, and ovariectomy be carried out separately for different forms of breast carcinoma. (73 refs.)

- 77-6120 **Unilateral Suckling and Breast Cancer (2 Letters to Editor).** (Eng.) MacMahon, B. (Dept. Epidemiology, Harvard Sch. Public Health, Boston, MA 02115); Trichopoulos, D.; Ing, R.; Ho, J. H.; Petrakis, N. L. *Lancet* 2(8039): 655-657; 1977.

Lactation cannot be assumed to have a protective effect against development of breast cancer. The custom of suckling only from the right breast may be connected to increased breast cancer in the left breast among Chinese houseboat dwellers later in the mother's life. Prolonged engorgement of the unsuckled breast may lead to abnormal change. (11 refs.)

- 77-6121 **Dietary Factors and Cancer of the Large Bowel.** (Eng) Reddy, B. S. (American Health Foundation, Valhalla, N. Y. 10595). *Semin Oncol* 3(4): 351-359; 1976.

Dietary factors involved in the incidence of cancer of the

large bowel are discussed. Increased incidence of this disease has been associated with an increased intake of dietary fat and beef and a decreased consumption of crude fiber and bulk-forming material. Experimental studies in man indicate that a high intake of fat affects the metabolic activity of the intestinal microflora, as well as the levels of certain fecal steroids, which can act as tumor promoters in the colon. Populations with a high rate of colon cancer, on a high fat, westernized diet, excreted higher levels of cholesterol and bile acid metabolites than did populations with a low rate of colon cancer. A study of the fecal constituents of patients with colon cancer, familial polyposis, polyps, and ulcerative colitis showed that the excretion of cholesterol metabolites and secondary bile acids was higher in the patients with colon cancer, polyps, and ulcerative colitis than in normal controls. No difference in the total fecal neutral sterol and bile acid concentration was observed between the patients and the normal controls. Rats maintained on a high fat diet and treated with 1,2-dimethylhydrazine (DMH) had a higher incidence of colon cancer than rats fed a normal diet and treated with DMH. Evidence indicates that dietary fat influences colon cancer pathogenesis and that control of passage, production, and metabolism of carcinogens, cocarcinogens or promoters are all involved in the induction and development of cancer of the colon. (49 refs.)

- 77-6122 **Fiber, A New Therapeutic Agent: Constipation, Biliary Lithiasis, Diverticulosis and Cancer of the Colon.** (Fre.) Bargheon, J. (No affiliation given). *Rev Fr Gastroenterol* (126): 5-10; 1977.

The incidence of digestive tract cancers has increased by 20% in the last two decades, and 75% of these lesions occur in the colon and rectum. It is suggested that this is due to the decreased consumption of raw cellulose fibers, and increased consumption of refined foods. The duration of movement through the gut of raw and refined food products and the frequency of gallstones as a function of diet and life style are discussed. The relationship between cholesterol and food fibers is reviewed. The physiological and biological role of cellulose fibers is presented, and the literature is briefly reviewed. (24 refs.)

- 77-6123 **Diet and Cancer.** (Eng.) Gori, G. B. (Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD 20014). *J Am Diet Assoc* 71(4): 375-379; 1977.

Diet may play an important role in the etiology of cancer in two ways: through ingestion of carcinogens or substances that are metabolized to carcinogens, or by establishing a condition that modulates organ susceptibility and response to cancer-causing agents. Particular emphasis is placed on the

association between fat intake and bowel cancer. Incidence and mortality data from the literature are reviewed. (36 refs.)

- 77-6124 **Geography of Cancer.** (Eng.) Blot, W. J. (Environmental Epidemiology Branch, NCI, Bethesda, MD 20014). *Sciences* 17(8): 12-15; 1977.

Cancer incidence varies greatly among populations in different areas of the world. Epidemiologic associations discussed include sunlight and skin cancer; industry, smoking, and lung cancer; snuff use and oral cancer; esophageal cancer, race, and diet; breast cancer and diet; and colon cancer, industrialization and diet. (no refs.)

- 77-6125 **The Epidemiology of Leukaemias and Lymphomas: A Review.** (Eng.) Kinlen, L. J. (Regius Dept. Medicine, Radcliffe Infirmary, Oxford, OX2 6HE, England). *Proc R Soc Med* 70(8): 553-556; 1977.

Contact and case-clustering studies on the suspected infectious etiology of Hodgkin's disease and leukemia are reviewed. Although the evidence is still inconclusive, the possibility of person-to-person transmission is suggested by some findings. Ionizing radiation and probably benzene are causes of leukemia. (28 refs.)

- 77-6126 **Some Variations in Childhood Cancers Throughout the World.** (Eng.) Davies, J. N. (No affiliation given). *Recent Results Cancer Res* 13: 28-58; 1976.

The differences in childhood cancers between countries are discussed in an epidemiologic review. For intracranial tumors and gliomas, differences in occurrence according to geographic area (environment) and race have been noted. With leukemia, different patterns occur in whites and blacks and in people of developed and less developed countries. Except for irradiation, causes are obscure. Links are suggested with malaria, maternal influenza, certain chromosomal abnormalities (congenital or acquired). Lymphosarcoma and histiocytic sarcomas are more common in areas of malnutrition and infection. The distribution of gonadal and endocrine tumors shows significant differences in Europe, East Africa and Brasil. Lymphomas frequently occur in many parts of Africa. Malaria, as well as the Epstein-Barr virus, may be involved in the pathogenesis of Burkitt's lymphoma. There is evidence that where malaria has been controlled, the incidence of Burkitt's lymphoma has rapidly

y fallen. Malnutrition may also have profound effects. Progressive and non-progressive histiocytoses can not easily be identified histologically or clinically nor are the boundaries, separating reaction from neoplasia, clearly defined. Sporadic nonfamilial retinoblastomas are most likely due to environmental factors. Nephroblastomas show the least variation in frequency all over the world. Many epithelial cancers of nonendocrine organs arise on the basis of some inherited metabolic defect. Adenocarcinoma of the vagina is associated with the use of a synthetic steroidal drug during pregnancy; the development of a cancer in the daughters may occur after a long latent period (12-24 yr). (136 refs.)

77-6127 **Lung Cancer. II. Epidemiology.** (Eng) Workshop on Lung Cancer (Geneva, Switzerland). *IUCC Tech Rep Ser* 25(3): 3-41; 1977.

Data on the epidemiology of lung cancer are reviewed. The closest association between smoking and lung cancer is found for cigarette smokers; pipe and cigar smokers also have an increased risk, but it is lower. This difference could be due to the fact that pipe and cigar smokers tend to inhale the smoke less deeply. Mortality is proportional to the number of cigarettes smoked, although the use of filters, less inhalation, and a reduction in puffs per cigarette may have a protective effect. The lung cancer death rate increases in proportion to the duration of smoking raised to the fourth power, indicating that it is more important than the number of cigarettes smoked. Risk of lung cancer decreases after cessation in smoke have not been identified, they are thought to be constituents of tar. Other agents known to cause lung cancer include coal combustion products, chrome and nickel ore, asbestos, mustard gas, ionizing radiation, arsenic bis(chloromethyl) ether, and chloromethyl methyl ether. Of these, asbestos, smoking, and possibly radiation have a synergistic effect. Epidemiological studies suggest that there is an urban factor involved in lung carcinogenesis that may be a reflection of occupational exposure, but other factors cannot be ruled out. One prospective study indicated that men with low vitamin A levels have a greater chance of contracting lung cancer than those with high vitamin A levels. A genetic factor has also been suggested to increase risk. Environmental radiation is estimated to cause about 1% of all cases of lung cancer. (119 refs.)

77-6128 **A New Concept of Tissue and Tumor Cell Proliferation.** (Eng) Gelfant, S. (Dept. Dermatology, Medical Coll. Georgia, Augusta, GA 30902). *Cancer Res* 37(11): 3845-3862; 1977.

A model of tissue and tumor cell proliferation is proposed based on the idea that cycling cells can be arrested in early G_1 by a G_0 block, in late G_1 by a G_1 block, or in late G_2 by a G_2 block. Four major categories of cells can be identified: cycling cells, noncycling G_1 -blocked cells, noncycling G_2 -blocked cells, and noncycling G_0 -blocked cells. These cells represent the potential proliferating pool both in culture and in tissues and tumors in vivo. The concepts and schemes of cycling and noncycling cells are reviewed, and a theory is proposed for the origin and recruitment of noncycling cells as a result of cellular aging. The concept of tissues and tumors as proliferate ecosystems, in which all tissues cooperate to fulfill the various requirements of the tissue or tumor, is introduced. (126 refs.)

77-6129 **Chemistry and Biosynthesis of Mucin Glycoproteins.** (Eng) Carlson, D. M. (Dept. Biochemistry, Purdue Univ., West Lafayette, IN 47907). *Adv Exp Med Biol* 89: 251-273; 1977.

The chemistry and biosynthesis of glycoproteins, particularly the mucous glycoproteins, are reviewed. The various topics include: carbohydrate-to-amino acid linkages, carbohydrate structural analysis, general aspects of protein and oligosaccharide biosynthesis, tracheobronchial mucous secretions, and ovarian cyst glycoprotein. Glycoproteins may play an important role in the loss of cellular characteristics following malignant transformation. (48 refs.)

77-6130 **Enzymatic Mechanisms of DNA Repair Processes.** (Rus) Tomilin, N. V. (Lab. Radiation Cytology, Inst. Cytology, USSR Acad. Sciences, Leningrad, USSR). *Tsitologiya* 19(10): 1086-1109; 1977.

Studies on the general biological and enzymatic mechanisms of DNA repair processes are reviewed, and the enzymes involved (endonuclease, exonuclease, DNA-polymerase and ligases) are considered. (117 refs.)

77-6131 **Molecular Basis of Plant Tumour Induction.** (Eng.) Lippincott, J. A. (Dept. Biology, Northwestern Univ., Evanston, IL). *Nature* 269(5628): 465-466; 1977.

A review is presented of tumor induction by *Agrobacterium tumefaciens*. It is suggested that the tumor may provide both the stimulus and the nutritional requirements for gene transfer in the agrobacteria; thus they may be the first cellular organisms shown to accomplish transfer and stable incorporation of foreign DNA into a eukaryotic cell. (22 refs.)

CHEMICAL CARCINOGENESIS

- 77-6132 **Alterations in DNA-dependent RNA Polymerases I and II from Rat Liver by Thioacetamide: Preferential Increase in the Level of Chromatin-associated Nucleolar RNA Polymerase IB.** (Eng) Leonard, T. B. (Dept. Pharmacology, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA 17033); Jacob, S. T. *Biochemistry* 16(20): 4538-4544; 1977.

The effect of a single injection of the hepatocarcinogen thioacetamide (TA, 50 mg/kg) on the levels of Sprague-Dawley rat liver RNA polymerases I and II was investigated. The enzymes in the bound (chromatin-associated) and free forms were separated and further purified by column chromatography. Within 24 hr of TA administration, the total units of bound RNA polymerases IA and IB were increased 3- to 4-fold as compared to control enzymes (derived from DNA equivalent nuclei). The stimulation of bound RNA polymerase IB was significantly greater than that of bound IA. The level of bound RNA polymerase II increased by only 30%-50% and free RNA polymerase I and II were relatively stable. TA did not significantly alter the size of the product synthesized by bound polymerase I. When similar units of the enzyme from the control and carcinogen-treated livers (rather than quantities of enzyme corresponding to the same DNA equivalent nuclei from these tissues) were assayed under conditions favoring one round of initiation, no significant difference in the levels of the bound RNA polymerase I was observed. These data suggest that TA-treated liver contains more enzyme molecules than control liver and consequently requires more DNA for saturation. There is a preferential increase in the level of bound RNA polymerase I over that of free enzyme, consistent with the proposed role of chromatin-associated polymerases in active transcription, which might explain the augmented ribosomal RNA precursor synthesis observed after TA administration. (40 refs.)

- 77-6133 **Effect of Thioacetamide on Liver Mitochondrial Enzymes - Carbamyl-P-synthetase and Ornithine Transcarbamylase.** (Eng) Feijoo, B. (Departamento de Bioquímica, Facultad de Farmacia, Madrid, Spain); Cascales, C.; Cascales, M.; Santos-Ruiz, A. *Proc Eur Soc Toxicol* 18: 262-264; 1977.

The effect of thioacetamide on urea cycle enzymes in the liver was studied in male Wistar rats inoculated ip with the compound at 50 mg/kg/day for 24-30 days. Urea levels and carbamyl-P-synthetase, ornithine transcarbamylase, and arginase activities decreased in the livers of the treated rats compared with controls. Moreover, thioacetamide produced a marked increase in ammonia concentration and an accom-

panying increase in glutamate dehydrogenase. Thus, the compound significantly disturbed the urea cycle and its ability to protect the cell against the toxic effect of ammonia accumulation. The relevancy of the thioacetamide-induced enzyme changes to the pathogenesis of liver diseases is discussed. (5 refs.)

- 77-6134 **Increased Incidence of Carcinoma of the Breast in Buffalo Strain Rats with One Kidney Ingesting N-4-(4'-Fluorobiphenyl)Acetamide.** (Eng) Reuber, M. D. (11014 Swansfield Rd., Columbia, MD 21044). *Z Krebsforsch* 87(2): 173-179; 1976.

The role of the kidney in breast carcinogenesis was studied in inbred Buffalo strain female rats fed N-4-(4'-fluorobiphenyl)acetamide (4'F-4BAA; 0.04% in the diet) for 36 wk. The rats were divided into two groups, one of which underwent uninephrectomy. Carcinomas of the breast were detected between 16 and 28 wk in intact rats and between 8 to 16 wk in nephrectomized rats. The incidence of carcinomas of the breast and of multiple carcinomas and poorly or undifferentiated carcinomas was greater in nephrectomized than in intact rats. These findings suggest that if toxic chemicals that are metabolized by the liver are not excreted by the kidney, their uptake could induce tumors in other organs. (14 refs.)

- 77-6135 **Possible Two-Stage Transplacental Liver Carcinogenesis in C57BL/6 Mice.** (Eng) Armuth, V. (Experimental Biology Unit, Weizmann Inst. Science, Rehovot, Israel); Berenblum, I. *Int J Cancer* 20(2): 292-295; 1977.

Two-stage carcinogenesis was attempted in C57BL/6 mice by maternal administration of 2-acetylaminofluorene (AAF) and neonatal injection of phorbol. The females were inoculated sc on day 15 of gestation with 0.5 ml of a 2% solution of AAF. After delivery, the young were given ip injections of phorbol [0.25 micromole (μ mol) 2 times/wk]; after weaning at 3 wk, the dose was doubled to 0.5 μ mol per injection and treatment was continued for 25 wk. There were six experimental groups: mothers inoculated with AAF on day 15; untreated mothers; untreated-offspring of untreated mothers; phorbol-treated offspring of untreated mothers; untreated offspring of AAF-treated mothers; phorbol-treated offspring of AAF-treated mothers. Three of 36 AAF-treated mothers developed

hepatomas, 2 developed reticulum cell sarcomas, and 1 developed a lung adenoma. The hepatomas were probably due to the AAF, and the sarcomas were probably spontaneous. Transplacentally, neither AAF nor phorbol alone increased tumor incidence. However, 8/74 phorbol-treated offspring of AAF-treated mothers developed hepatomas compared to 2/70 untreated offspring of AAF-treated mothers. The histology of the induced tumors is presented. (12 refs.)

7-6136 Persistent Fine Structural Changes Induced by Single Doses of Carcinogens in Rat Hepatocytes (Meeting Abstract). (Eng) Flaks, B. (Dept. Pathology, Univ. Bristol, Medical Sch., Bristol, England). In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 77; 1977. (no refs.)

7-6137 Secondary Structural Modifications as a Consequence of In Vitro Acetylation and Phenanthrylation of DNA by the Ultimate Carcinogen N-Acetoxy-N-2-cetylaminophenanthrene. (Eng) Lang, M. C. (Laboratoire de Biophysique, Institut de Biologie Moléculaire et Cellulaire du Centre National de Recherche Scientifique, 15, rue Descartes, 67084 Strasbourg Cedex, France); Fuchs, R. P.; Maune, M. P. *Cancer Res* 37(11): 3887-3891; 1977.

The phenanthrylation and acetylation of DNA were studied during its reaction with N-acetoxy-N-2-cetylaminophenanthrene (N-AcO-AAP) in vitro. Since native and heat-denatured DNA's reacted equally in all buffers used, phenanthrylation was not dependent on the secondary structure of the DNA. However, acetylation was strongly dependent on the secondary structure, since acetylation of heat-denatured DNA was 5 to 10 times greater than that of native DNA in all buffers used. However, when the reaction took place in 0.01 M sodium citrate buffer at pH 7, the degree of acetylation was four times lower than that of phenanthrylation. The sites at which alkylation occurs have not yet been identified. The dynamic structure of the DNA did not favor acetylation, suggesting that at least some acetylation sites are normally accessible in the double helix. Thermal destabilization of the double helix was studied, and an attempt was made to link it to phenanthrylation. (17 refs.)

7-6138 Carcinogen Control in the Urine of Dogs During Bladder Carcinogenesis (Meeting Abstract). (Eng) Gericke, D. (HOECHST AG, Univ. Tübingen, Tübingen, W. Germany); Harzmann, R.; Bichler, K. H.; Grottsch, I. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency

for Research on Cancer. (Lyon, France): p. 81; 1977. (no refs.)

77-6139 The Role of the Promoter L-Tryptophan on Tumorigenesis in the Urinary Bladder. 2. Urinary Bladder Carcinogenicity of FANFT (Initiating Factor) and L-Tryptophan (Promoting Factor) in Mice. (Jpn) Matsushima, M. (Dept. Urology, Sch. Medicine, Toho Univ., Japan). *Jpn J Urol* 68(8): 731-736; 1977.

The tumor-promoting effect of L-tryptophan in urinary bladder carcinogenesis was investigated in 60 D-D female mice who were fed a CE-2 diet containing 0.1% N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) for 4 wk. These mice were then divided into two groups: one received 0.2% L-tryptophan in the diet for 56 wk and the other received diet only. Two bladder tumors were noted in the 30 mice who received L-tryptophan. Both the labeling index and hyperplastic index were significantly different between the two groups. These results indicate the promotion of urinary bladder tumorigenesis by L-tryptophan. (22 refs.)

77-6140 The Role of the Promoter L-Tryptophan on Tumorigenesis in the Urinary Bladder. I. Study of Urinary Tryptophan Metabolites. (Jpn) Matsushima, M. (Dept. Urology, Sch. Medicine, Toho Univ., Japan). *Jpn J Urol* 68(8): 720-730; 1977.

Excretion of the urinary tryptophan metabolites kynurenine and 3-hydroxykynurenine was measured before and after administration of 3 g of L-tryptophan to men with spontaneous bladder tumors (28), men with occupational bladder tumors (12), dyestuff workers (9), and 39 healthy men and women (controls). In the controls, values before L-tryptophan administration were low, but after administration, women had much higher values, especially those who had recently gone through menopause. Thus, only the men were used as controls. All tumor patients and dyestuff workers had significantly higher preadministration values than controls. However, postadministration values minus preadministration values were not significantly different. Postadministration plasma tryptophan levels in spontaneous bladder tumor patients were lower than those of controls; exact measurement of the metabolite values was not possible. Metabolite levels following administration of 3 g L-tryptophan did not differ significantly from those following administration of 1 g. (56 refs.)

77-6141 Synthesis of a Mutagenic Principle Isolated from Tryptophan Pyrolysate. (Eng) Takeda, K.

(Faculty Pharmaceutical Science, Univ. Tokyo, Hongo, Bunkyo-ku, Tokyo, Japan); Ohta, T.; Shudo, K.; Okamoto, T.; Tsuji, K.; Kosuge, T. *Chem Pharm Bull (Tokyo)* 25(8): 2145-2146; 1977.

A procedure is reported by which 3-amino-1-methyl-5H-pyrido[4,3-b]indole, a mutagen isolated from tryptophan pyrolysate, was synthesized. This procedure can be used to provide material for further carcinogenicity studies. (3 refs.)

77-6142 Ligandin and Protein A: The Possible Roles of These Proteins in Haem and Carcinogen Metabolism (Meeting Abstract). (Eng) Ketterer, B. (Courtauld Inst. Biochemistry, Middlesex Hosp. Medical Sch., London W1P 7PN, England); Tipping, E.; Srai, K. S. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 80; 1977. (no refs.)

77-6143 Induction of Hepatic Tumors in a Teleost (*Oryzias latipes*) after Treatment with Methylazoxymethanol Acetate: Brief Communication. (Eng) Aoki, K. (Div. Biology, Natl. Inst. Radiological Sciences, Anagawa, Chiba-shi 280, Japan); Matsudaira, H. *J Natl Cancer Inst* 59(6): 1747-1749; 1977.

Exposure of medakas (*Oryzias latipes*) to concentrations of 0.1 to 3 ppm methylazoxymethanol acetate in the aquarium water for periods ranging from 1 to 120 days resulted in tumor formation in fish of all groups within 3 to 5 mo. The liver neoplasms included trabecular hepatoma and cholangioma. (11 refs.)

77-6144 An Electron Microscopic Study of Mouse Epidermis after a Single Subcutaneous Injection of Thiophene Free Benzene. (Eng) Bhisey, R. A. (Cancer Res. Inst., Parel, Bombay-400 012, India); Sirsat, S. M. *Indian J Cancer* 14(1): 10-17; 1977.

The effects of a 0.2 ml sc dose of thiophene free benzene on mouse epidermis were investigated to determine the action of this solvent for experimental doses of carcinogenic polycyclic hydrocarbons. Condensation of nuclear chromatin and fewer cell organelles were observed within 24 hr. Long term effects included condensation of tonofibrils, gaps in basal lamina, and basement membrane-like material in subepidermal areas. There were no membrane coating granules in the keratinocytes. (24 refs.)

77-6145 Benzene and Leukaemia (Two Letters to Editor). (Eng) Tabershaw, I. R. (10215 Fernwood Road, Suite 302, Bethesda, MD 20034); Lamm, S. H.; Infante, P. F.; Rinsky, R. A.; Wagoner, J. K.; Young, R. J. *Lancet* 2(8043): 867-869; 1977.

It is suggested that the relative risk of leukemia among workers exposed to benzene at two pliofilm plants was incorrectly estimated from the distribution of leukemia types. In a reply to this suggestion, it is maintained that a true excess risk of acute myelogenous and monocytic leukemia was demonstrable among the two cohort populations. (16 refs.)

77-6146 Metabolism of Promutagenic and Procarcinogenic Safrole and Related Compounds (Meeting Abstract). (Eng) Levi, P. (ERA CNRS 267, URR de Medecine, Universite de Dijon, 21033 Dijon, France); Janiaud, P.; Delaforge, N.; Dorange, J. L.; Padieu, P. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 66; 1977. (no refs.)

77-6147 Failure of Ascorbic Acid to Inhibit the Metabolic N-Oxidation of the Bladder Carcinogen 4-Biphenylamine. (Eng) Brill, E. (Dept. Pharmacology, Univ. Miami Sch. Medicine, Miami, FL 33152); Radomski, J. *Res Commun Chem Pathol Pharmacol* 16(1): 85-94; 1977.

The effect of pretreatment and concomitant feeding of large loading doses of L-ascorbic acid (AA) on the microsomal N-oxidation of 4-biphenylamine (BPA) and on the urinary concentration of its metabolites was investigated in dogs. Each of four dogs (3 females, 1 male) received 80 mg/kg/day AA po for 15 days. On the day of the experiment, each dog received 5 mg/kg BPA concomitantly with 80 mg/kg AA. The urines were collected by catheterization and the metabolic N-oxidation products determined by gas chromatography. When the dogs received AA and 4-BPA they showed no significant difference in N-oxidized metabolites compared with when they received BPA alone. The results indicate that pretreatment with large doses of AA has no effect on the metabolic N-oxidation of BPA or on the urinary concentration of these metabolites. Failure of AA to reduce the N-arylhydroxylamine metabolite concentration when these metabolites are conjugated may explain its inability to prevent N-(4-(5-nitro-s-furyl)-2-thiazolyl)formamide - induced bladder cancer in mice. These results cast doubt on the efficacy of AA in bladder tumor prophylaxis. (19 refs.)

77-6148 High-Pressure Liquid Chromatographic and Other Assays for Biphenyl Hydroxylation Com

pared. (Eng) Burke, M. D. (Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England); Benford, D. J.; Bridges, J. W.; Parke, D. V. *Biochem Soc Trans* 5(5): 1370-1372; 1977.

A high-pressure liquid chromatography assay for microsomal biphenyl metabolites measured a minimum of 0.02 nanomole (nmol) 2-, 3-, or 4-hydroxybiphenyl, 0.01 nmol 2,2'-dihydroxybiphenyl, and 0.05 nmol 4,4-dihydroxybiphenyl in incubation mixtures of biphenyl and rat liver microsome fractions. Although the assay was more time-consuming than the standard fluorimetric assay, it was equally sensitive and free from interference by metabolites of carcinogens such as benzo(a)pyrene. (4 refs.)

77-6149 **Radiographic Evaluation of Gastric Hyperplasia Induced by Polychlorinated Biphenyls (Meeting Abstract).** (Eng) Rosenquist, C. J. (Dept. Radiology, Univ. California, Davis, CA); Silverman, S. *Invest Radiol* 12(5): 401; 1977. (no refs.)

77-6150 **Possible Pitfalls of the Biphenyl Test for Chemical Carcinogens.** (Eng) Tong, S. (Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England); Ioannides, C.; Parke, D. V. *Biochem Soc Trans* 5(5): 1372-1374; 1977.

When incubated with a rat liver microsome suspension in the presence of an NADPH-generating system, safrole formed a metabolite that fluoresced at 338 nanometers (nm), the wavelength used for the determination of 2-hydroxybiphenyl. Microsomal suspensions from rats pretreated with phenobarbital resulted in higher fluorescence at 338 and 415 nm, the wavelengths used for the determination of 4-hydroxybiphenyl. Stimulation of the 2-hydroxylation of biphenyl by safrole could give rise to false positives in the biphenyl test for carcinogens. (10 refs.)

77-6151 **Safe Flame Retardant. Toxicological Data Presented for Caliban F/R 44 Textile Flame Retardant.** (Eng) Mischutin, V. (White Chemical Corp., Bayonne, NJ). *Am Dyest Rep* 66(11): 51-55, 52; 1977.

The toxicity data on the components of the flame retardant Caliban F/R-44, and aqueous dispersion of decabromodiphenyl ether and antimony trioxide (AO), are presented. DBDPO (decabromodiphenyl oxide) induced transient eye irritation in albino rabbits, but did not damage the cornea, iris and lens. Thirty days feeding of doses of 800, 80, or 8 mg/kg to male Sprague-Dawley rats resulted in liver enlargement and minor liver and kidney lesions in rats fed 800 mg/kg/day and in thyroid hyperplasia in rats fed 800 and 80 mg/kg/day.

Two yr administration of 1.0, 0.1, or 0.01 mg DBDPO/kg body wt/day in the diet of Sprague-Dawley rats produced low-level, steady state concentrations of bromine in the liver and a time and dose-related increase of bromine in the adipose tissue, but no carcinogenic effects. No teratogenic effects were demonstrable for DBDPO. AO trioxide was minimally irritating to the skin of rats and extremely irritating to the eyes of rabbits. Exposure to an 8 mo diet of 2% AO resulted in appreciable accumulation of antimony in the tissue and blood (particularly in the thyroid) 40 days after removal from the AO diet; no disturbance in function was seen. Human studies with AO have not revealed any irritation or other pathology. It is concluded that the materials in this flame retardant are safe for human use. (12 refs.)

77-6152 **Elemental Analysis of a Tumor from a Nocturnal Prosimian with Special Emphasis on Bromine.** (Eng) Cowgill, U. M. (Dept. Biology, Univ. Pittsburgh, Pittsburgh, PA 15260). *Sci Total Environ* 7(1): 63-69; 1977.

A naturally occurring myeloliposarcoma removed from a 15-yr-old female *Perodicticus potto* was analyzed chemically by x-ray emission and optical emission techniques for the solid material and by thin-layer chromatography for the oily material. The tumor oil consisted primarily of triglycerides; other compounds were cholesteryl ester, free fatty acids, cholesterol, and diglycerides. No sterol esters or glyceryl ether diesters were detected. Of the 32 elements detected, only the bromine concentration was unexpectedly high. It was also unexpectedly high in the only available embryonic tissue (placenta) from the same animal, and in other tumor analyses reported in the literature. These observations substantiated the previous suggestion that tumor tissue chemically resembles embryonic tissue. Using liver as a reference, Br is enriched relative to the other halogens in the human ovary and relative to iodine and fluorine in the human testes. (22 refs.)

77-6153 **About the Influence of Halogenated Pyrimidines on the In Vivo-Oncogenesis.** (Eng) Gericke, D. (Hoechst A. G., Frankfurt/Main, W. Germany). *Necplasma* 24(3): 263-269; 1977.

The influence of halogenated pyrimidines on in vivo carcinogenesis in an inbred strain of female albino mice was investigated. Treatment of mice with 0.02 or 0.05 mg 20-methylcholanthrene (20-MC) sc and, 24 hr later, 71 or 110 injections of 200 mg/kg 5'-iododeoxyuridine (IUdR) or 450 mg/kg 5'-bromodeoxyuridine (BUdR) sc did not enhance tumor formation after 76 wk. Studies of the transplantation of tumor tissue had varying results, but they argued against the virus-inducing ability of BUdR. The effect of BUdR on the development of Friend leukemia virus was studied in mice receiving an ip injection of a spleen suspension. The mice

received 9.0, 0.9, or 0.45 mg/20 g BUdR for 5 days followed by a 2-day interval, for a total of three courses. Splenomegaly was inhibited only at the largest dose; however, splenomegaly increased rapidly in all groups upon cessation of treatment. Syrian hamsters were treated with a 0.2% cell-free extract of an amelanotic melanoma and then with 10 injections of 180, 18, or 1.8 mg/kg BUdR; BUdR had no effect. Treatment of susceptible hosts with cell-free extracts of the melanoma and with 10 of the above BUdR doses or 26 injections of 80 mg/kg IUdR or BUdR failed to induce melanomas. It is concluded that halogenated pyrimidines do not stimulate 20-MC carcinogenesis and that BUdR and IUdR do not stimulate hosts to complete incomplete forms of viruses. (18 refs.)

- 77-6154 **Comparative Metabolism of Haloethers.** (Eng) Smith, C. C. (Dept. Environmental Health, Univ. Cincinnati Coll. Medicine, Cincinnati, OH 45267); Lingg, R. D.; Tardiff, R. G. *Ann NY Acad Sci* 298: 111-123; 1977.

Various metabolic parameters were measured in female Charles River CD rats and female rhesus monkeys given 3, 30, or 300 mg/kg bis(2-chloroisopropyl ether) (BCIE) by various routes. Differences in tissue levels of BCIE were observed between these species, especially concentrations in the liver, gastrointestinal tract, brain, and muscle mass following a single parenteral dose of 30 mg/kg. The rat excreted two times more urinary BCIE at this dose than the monkey, although excretion was complete in both species by 24 hr. (8 refs.)

- 77-6155 **Differential Toxicity of Chloroform in the Mouse.** (Eng) Hill, R. N. (Dept. Pharmacology, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA 17033). *Ann NY Acad Sci* 298: 170-176; 1977.

Genetic differences in murine sensitivity to chloroform were demonstrated. The LD₅₀ was 0.08 mg/kg for sensitive DBA mice, 0.33 mg/kg for resistant C57BL/6J mice, and 0.20 mg/kg for their F₁ hybrids. DBA mice were also more susceptible to renal toxicity, being unable to repair damaged renal tubules. An absolute sex-related difference was observed regarding kidney damage. Androgens play a significant role in this difference and in death due to chloroform and, possibly, the strain-related difference in sensitivity to kidney damage. (52 refs.)

- 77-6156 **Increased Incidence of Neoplasms in Rats Exposed to Low Levels of 2,3,7,8-Tetrachlorodibenzo-p-dioxin.** (Eng) Van Miller, J. P. (Dept. Pathology, Univ. Wisconsin, Madison, WI 53706); Lalich, J. J.; Allen, J. R. *Chemosphere* 6(10): 625-632; 1977.

The toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was investigated in groups of 10 male Sprague-Dawley rats fed 1, 5, 50, or 500 parts per trillion (ppt; 10⁻¹² g TCDD/g food) or 1, 5, 50, 500, or 1,000 ppb (10⁻⁹ g TCDD/g food). Animals receiving 50, 500, or 1,000 ppb TCDD died between the second and fourth week of the experiment. Autopsy revealed liver necrosis, cellular proliferation in the bile ducts, and decreased spermatogenesis. The overall incidence of neoplasms in the remaining six groups fed subacute levels of TCDD was 38% (23 animals), with no neoplasms observed in the 1-ppt group. There were 6 neoplasms in the animals fed 5 ppt (ear duct carcinoma, lymphocytic leukemia, adenocarcinoma of the kidney, malignant peritoneal histiocytoma with metastases, angiosarcoma of the skin, and Leydig cell adenoma), 3 in those fed 50 ppt (muscle fibrosarcoma, squamous cell skin tumor, brain astrocytoma), 4 in rats fed 500 ppt (muscle fibroma, skin carcinoma, kidney adenocarcinoma, and sclerosing seminoma), and 5 in animals fed 1 ppb (cholangiocarcinoma, cutaneous angiosarcoma, brain glioblastoma, 2 malignant peritoneal histiocytomas with metastases). There were 10 neoplasms in 7/10 animals fed 5 ppb (4 squamous cell lung tumors, 4 neoplastic liver nodules, and 2 cholangiocarcinomas). No neoplasms were observed in controls. (15 refs.)

- 77-6157 **Formation of Imidazol Derivatives of Nucleic Acid Bases (DNA and RNA) by Metabolites of Vinyl Chloride In Vivo and In Vitro (Meeting Abstract).** (Eng) Laib, R. J. (Inst. Toxicology, Tübingen, W. Germany); Bolt, H. M. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 84; 1977. (no refs.)

- 77-6158 **The Metabolism of Styrene Oxide in the Isolated Perfused Rat Liver. Identification and Quantification of Major Metabolites.** (Eng.) Ryan, A. J. (Pharmacology Branch, Natl. Inst. Environmental Health Sciences, P. O. Box 12233, Research Triangle Park, NC 27709); Bend, J. R. *Drug Metab Dispos* 5(4): 363-367; 1977.

The metabolism of styrene oxide was investigated in isolated perfused male Sprague Dawley rat liver. ¹⁴C-styrene oxide (100 μmoles, 1 μCi) in acetonitrile (500 μliters) was added to the perfusate and recirculated for 90 min. Bile samples were taken at various intervals. Max excretion of the dose was observed after 25 min; by 90 min, excretion had ceased. Most of the radioactivity was isolated in a single compound: S-(1-phenyl-2-hydroxyethyl)glutathione. Approx equal amounts of styrene glycol, mandelic acid and S-(1-phenyl-2-hydroxy)glutathione were found in the circulating perfusate. The findings indicate that at the dose administered, styrene oxide is efficiently and approx equally metabolized by both the hydratase and glutathione-conjugating pathways. It is not

known if similar results should be expected with styrene, a potential alkylating agent. (15 refs.)

- 77-6159 **Malignant Transformation of a Baby Hamster Lung Cell Line by 2-Chlorobutadiene (Meeting Abstract).** (Eng) Papadopoulos, D. (Fondation Curie-Institut du Radium, 26 rue d'Ulm, 75005 Paris, France); Markovits, P.; Beesau, O.; Hubert-Habart, M. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 78; 1977.

- 77-6160 **The Metabolism of Aramite, a Pesticide Inducing Liver Tumors.** (Eng) Truhaut, R. (Laboratoire de Toxicologie, Faculte des Sciences Pharmaceutiques et Biologiques, Paris, France); Claude, J. R.; Blanc, F. *Proc Eur Soc Toxicol* 18: 326-328; 1977.

The metabolism of Aramite (sulfurous acid 2-(p-tert-butylphenoxy)-1-methylethyl-2-chloroethyl ester) was studied in male Wistar rats. In an acute toxicity study, the animals received 2 g/kg by a stomach tube at a rate of 1 ml/100 g. In a chronic toxicity study, the rats were fed a diet containing 5 g/kg Aramite for 56 wk; the daily total dose of Aramite was 400 mg/kg. Urine samples were collected, extracted with ethyl acetate, and analyzed by thin- and thick-layer chromatography. Two metabolites, but not Aramite itself, were found in the urine of the chronic and acute toxicity animals. The main metabolite was identified as 1-(p-tert-butylphenoxy)-2-propanol, with a mol wt of 208. This indicated that Aramite was metabolized by hydrolysis. In vitro experiments in which gastric conditions were simulated indicated that hydrolysis does not occur in the stomach. (5 refs.)

- 77-6161 **Study on the Carcinogenicity of 2,4,5-T in Mice (Meeting Abstract).** (Eng) Muranyi-Kovacs, I. (U.119 de l'INSERM, 27, Bd Lei Roure, 13009 Marseille, France); Rudali, G.; Imbert, J. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 64; 1977. (no refs.)

- 77-6162 **Enhancement of Urethan Tumorigenesis in Mouse Lung by Butylated Hydroxytoluene.** (Eng) Witschi, H. (Departement de Pharmacologie, Faculte de Medecine, Universite de Montreal, Montreal, Quebec, Canada); Williamson, D.; Lock, S. *J Natl Cancer Inst* 58(2): 301-305; 1977.

The possibility of enhancing urethane tumorigenesis in the

mouse lung by repeatedly producing type II cell proliferation with butylated hydroxytoluene (BHT) was investigated. BHT injection (400 mg/kg ip) produced cell proliferation in mouse lungs within 2-4 days. No other antioxidant tested (butylated hydroxyanisole, pyrogallol, propylgallate, thiodipropionic acid, α -tocopherol, and ascorbic acid) induced cell proliferation. Male Swiss-Webster mice were treated with 1 mg urethane/g before, during, or after BHT-stimulated cell proliferation. The number of developing tumors was not affected in any of the schedules. It was possible, however, to enhance tumor formation in Swiss-Webster and A/J mice by repeated weekly injections of BHT beginning 7 days after a single dose of urethane. Weekly injections of BHT into mice pretreated with 0.9% NaCl reduced the number of spontaneous pulmonary adenomas. It is suggested that enhancement of tumorigenesis by BHT might be brought about by repeated proliferation of the target cells once the tumorigenic process has been initiated by urethane. (36 refs.)

- 77-6163 **Cell Kinetics of Urethane-induced Murine Pulmonary Adenomas: III. Implications of the Disparity Between the Rates of Entry into DNA Synthesis and into Mitosis.** (Eng.) Dyson, P. (Dept. Pathology, Univ. Newcastle upon Tyne, Newcastle upon Tyne, England); Heppleston, A. G. *Br J Cancer* 36(2): 215-220; 1977.

Metaphase arrest by vincristine (1 μ g/g, ip) in urethane-induced pulmonary adenomas in male A2G mice became linear after 60 min. The rate of entry into metaphase was 0.191%/hr. The duration of prophase plus metaphase was calculated to be 1.7 hr. A growth fraction of 9% and a cell-loss factor of 52% were derived. The DNA profiles showed an increased frequency of hyperdiploid nuclei with age. Circumstantial evidence for polyploidy was provided by the presence of many binucleate cells in the tumors. It is suggested that these cells may represent a stage in the development of polyploidy, and the relevance of these findings to neoplastic transformation is discussed. (21 refs.)

- 77-6164 **Ethylation and Metabolism of Ethionine (Meeting Abstract).** (Eng) Brada, Z. (Papanicolaou Cancer Res. Inst., Miami, FL 33123); Altman, N. H.; Bulba, S. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 86; 1977. (no refs.)

- 77-6165 **The Disturbance of Oxidative Phosphorylation in Rat Liver Mitochondria by the Carcinogens 12-Hydroxystearic Acid and Its Methyl Ester.** (Eng) Hadler, H. I. (Dept. Chemistry and Biochemistry,

Southern Illinois Univ., Carbondale, IL); Mueller, K. W. *J Environ Path Toxicol* 1(1): 75-85; 1977.

The carcinogens 12-hydroxystearic acid and its methyl ester disrupted oxidative phosphorylation in rat liver mitochondria. The in vitro mitochondrial effects induced by the agents included uncoupled respiration, ATPase activity, and energized volume changes linked either to respiration or ATP. Mitochondria mediated the enzymic conversion of the ester to the acid. Conversion was retarded by the thiol reagent showdomycin. These data, in conjunction with previous reports dealing with other carcinogens and their derivatives, contribute to an experimental confluence between oxidative phosphorylation and chemical carcinogenesis. (20 refs.)

- 77-6166 **Species and Rat Strain Variation in Pancreatic Nodule Induction by Azaserine.** (Eng) Roebuck, B. D. (Dept. Pathology, Dartmouth Medical Sch., Hanover, NH 03755); Longnecker, D. S. *J Natl Cancer Inst* 59(4): 1273-1277; 1977.

The susceptibility of Wistar (outbred), W/LEW and F344 rats, Charles River CD-1 (outbred albino) mice, Syrian golden hamsters (outbred) and strain 13 guinea pigs to atypical acinar cell nodule (AACN)-induction by azaserine was examined. Experiments in which single ip doses of 60 and 80 mg/kg were administered to Wistar rats revealed that 60 mg/kg was the max dose tolerated. Experiments with Wistar rats receiving 20 to 60 mg/kg injections of azaserine to a total dose of 120 to 200 mg/kg over 2 to 5 wk revealed that nodule counts in groups receiving weekly injections for 4 to 5 wk were comparable to those in groups receiving twice weekly injections even though the latter received more azaserine. In hamsters treated with 25 mg/kg injections for 6 wk to a total of 150 mg/kg, 4/4 animals developed tumors with a mean of 1.8 nodules/pancreas. In guinea pigs receiving 10 or 30 mg/kg injections for 6 wk to total doses of 60 and 180 mg/kg, respectively, 2-3/8 and 2-5/10 animals developed tumors with means of 0.4 nodules/pancreas for both groups. For mice receiving 10 or 30 mg/kg injections for 5 wk to a total dose of 50 and 150 mg/kg, respectively, 10/10 and 9/9 animals developed tumors with means of 9.3 and 9.4 nodules/pancreas. For male and female F344 rats receiving 20 mg/kg doses over 8 wk to a total dose of 150 mg/kg, 5/5 and 10/11, respectively, developed tumors with means of 8.7 and 5.0 nodules/pancreas. For male and female Wistar rats receiving 20 mg/kg doses for 6 wk to a total dose of 120 mg/kg, 9/9 and 6/6 animals developed tumors, respectively, with means of 101.3 and 24.5 nodules/pancreas. In male and female W/LEW rats receiving 30 mg/kg for 5 wk to a total dose of 150 mg/kg, 20/20 rats of both sexes developed tumors with means of 87.1 and 43.8 nodules/pancreas, respectively. Administration of the same doses for 10 wk to a total of 300 mg/kg resulted in tumor induction in 8/8 and 9/9 male and female rats, respectively, with means of 117.9 and 87.4 nodules/pancreas. It is recommend-

ed that male W/LEW rats be used to study azaserine induced pancreatic carcinomas. (16 refs.)

- 77-6167 **DNA Damage and Repair in Rat Tissues Following Administration of Azaserine.** (Eng) Lilja, H. S. (Dept. Pathology, Dartmouth Medical Sch., Hanover, NH 03755); Hyde, E.; Longnecker, D. S.; Yager, J. D. *Cancer Res* 37(11): 3925-3931; 1977.

Alkaline sucrose gradients were used to determine DNA damage and repair in the tissues of azaserine (AS)-treated Wistar and Wistar/Lewis rats. Wistar rats sacrificed 1 hr after 30 mg/kg AS ip had damaged DNA in the pancreas, liver, and kidney. Partial DNA repair was apparent at 1 wk. At 4 wk the DNA sedimentation profiles were unchanged from 1 wk, indicating persistent damage in all three tissues. Variable damage was observed in pancreatic DNA from animals treated with 3 and 10 mg/kg, with less damage at 3 mg/kg. At 1 mg/kg, AS had a minimal effect on the pancreatic DNA of Wistar rats. All Wistar/Lewis rats given 3 or 10 mg/kg and sacrificed 1 hr later exhibited a uniform response to AS. Damage to pancreatic DNA was extensive and similar at the two dose levels, and it resembled that observed in Wistar rats 1 hr after 30 mg/kg AS. The extent of DNA repair was similar in the pancreas, liver, and kidney 1 or 4 wk after 10 mg/kg AS; it was comparable to that detected in Wistar rats at the same intervals following a 30 mg/kg dose. Pancreatic, liver, and kidney DNA from animals treated at 10 mg/kg and sacrificed at 9 wk sedimented like the DNA from corresponding controls, as did pancreatic and liver DNA from animals treated at 3 mg/kg and sacrificed at 4 wk. Problems in establishing the relationship between the DNA damage caused by AS and its carcinogenic potential are discussed. (20 refs.)

- 77-6168 **Induction of Tumors in Mice with the Herbicide Succinic Acid 2,2-Dimethylhydrazide.** (Eng) Toth, B. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NB 68105); Wallcave, L.; Patil, K.; Schmeltz, I.; Hoffmann, D. *Cancer Res* 37(10): 3497-3500; 1977.

Beginning at age 8 wk, random-bred Swiss albino mice received 2% succinic acid 2,2-dimethylhydrazide (SADH) in their drinking water for life. The treatment gave rise to tumors of the blood vessels, lungs, and kidneys. The tumor incidences in these tissues in the controls were 6%, 18%, and 0%, compared with 73%, 73%, and 5% in the treated rats. Light microscopy revealed typical angiomas and angiosarcomas of the blood vessels, adenomas and adenocarcinoma of the lungs, and adenomas of the kidneys. The study demonstrates the carcinogenicity of SADH. Since the residues of this chemical are found in fruit, many humans are exposed to it. The environmental implication of this finding and the properties of hydrazine analogs are discussed. (23 refs.)

- 77-6169 **Prolonged Survival and Decrease in Intestinal Tumours in Dimethylhydrazine-treated Rats Fed a Chemically Defined Diet.** (Eng) Castleden, W. M. (Dept. Surgery, St. Bartholomew's Hosp., London, England). *Br J Cancer* 35(4): 419-495; 1977.

The effects of different diets on tumorigenesis in male Wistar rats receiving 10 or 20 mg 1,2-dimethylhydrazine (DMH) kg body wt/wk were investigated. The rats were fed either Milne's laboratory diet (standard); standard plus either duphalac in water, guar gum, pectin, normacol or metamucil; or an elemental diet (Vivonex). Analysis of the bowel tumors in rats receiving 20 mg/kg/wk indicated that all 10 on the elemental diet survived the 24 wk experiment (400 mg/kg DMH/rat). The observed/expected tumor ratios were high in all groups except those fed the standard diet, the standard diet plus duphalac, or the elemental diet. For rats fed 10 mg/kg/wk, the observed/expected tumor ratios were high for all groups except those on the standard plus duphalac diet, standard plus normacol diet, or the elemental diet. The combined results at the two doses indicate that the elemental diet not only protected against DMH toxicity at the higher doses, but also significantly reduced the incidence of small and large bowel tumors at both doses. The freely available elementary diet could be useful in carcinogenesis experiments involving controlled alterations in diet. (12 refs.)

- 77-6170 **Increased Invasiveness of Colonic Carcinomas Induced by Dimethylhydrazine in Rats with Partial Small-bowel Resection.** (Eng) Tilson, M. D. (Dept. Surgery, Yale Univ. Sch. Medicine, New Haven, CT); Buck, M.; Livstone, E. M.; Sheahan, D. G. *Surg Forum* 28: 139-140; 1977.

Small-bowel resection (SBR) significantly increased the number of invasive colonic carcinomas in Sprague-Dawley rats treated with dimethylhydrazine (DMH, 20 mg/kg/wk, sc). At 5 mo, the mean number of tumors per animal was 0.12 in animals subjected to DMH alone and 2.60 in animals subjected to DMH + SBR. The promotion of chemical carcinogenesis by SBR may be related to its effect on crypt proliferation. (3 refs.)

- 77-6171 **Cell Proliferation in the Colon of Carcinogen-treated Rats and in Chemically Induced Colonic Carcinoma (Meeting Abstract).** (Eng) Tutton, P. J. (Dept. Anatomy, Monash Univ., Clayton, Vic 3168, Australia); Barkla, D. H. *J Anat* 124(2): 518; 1977. (no refs.)

- 77-6172 **Tumor Induction Studies with Hydrazine Derivative Ingredients of Mushrooms, *Agaricus Bisporus* and *Gyromitra Esculenta* (Meeting Abstract).**

(Eng) Toth, B. (Eppley Inst., Univ. Nebraska Medical Center, Omaha, NB 68105). In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 68; 1977. (no refs.)

- 77-6173 **Safety Examination of Some Edible Plants, Part 2.** (Eng) Hirono, I. (Dept. Pathology, Gifu Univ. Sch. Medicine, Gifu-City 500, Japan); Mori, H.; Kato, K.; Ushimaru, Y.; Kato, T.; Haga, M. *J Environ Pathol Toxicol* 1(1): 71-74; 1977.

Inbred ACI rats were used to determine the carcinogenicity of cacalia, dandelion, ostrich fern, and aralia, which are used as human food or in folk medicines, and of burdock, bamboo shoots, and lotus, which are cultivated as vegetables in Japan. Fresh plant materials were dried, milled, and administered as 4%-33% of the basal diet for > 120 days. None of the plants exhibited any carcinogenic activity. (7 refs.)

- 77-6174 **Inhibition of Hepatocarcinogenesis by Adrenocorticotropin in Aflatoxin B₁-treated Rats.** (Eng) Chedid, A. (Dept. Pathology, Univ. Health Sciences/Chicago Medical Sch., 2020 W. Ogden Ave., Chicago, IL 60612); Bundeally, A. E.; Mendenhall, C. L. *J Natl Cancer Inst* 58(2): 339-349; 1977.

The effects of adrenocorticotropin (ACTH), growth hormone (GH), and insulin on aflatoxin B₁ (AFB₁) carcinogenesis were studied in inbred Fischer 344 rats. All rats received 125 µg AFB₁ po weekly. One group also received 1 unit (U) GH/wk sc for 10 wk, another received 4 U ACTH/wk for 20 wk, and a third group received 0.5 U insulin/wk sc for 20 wk. A fourth group received no hormone. Animals in each group were killed at 7, 14, 21, 28, 35, and 77 wk, and their livers were examined by light and electron microscopy. Animals receiving AFB₁ + ACTH did not develop hepatocellular carcinomas, but 3/6 males that survived 56 wk developed malignant lymphoma. Hepatocellular carcinoma developed in all animals given AFB₁ alone or in combination with insulin or GH. Animals that received AFB₁ + GH developed unusually large tumors, but in those that received AFB₁ + insulin, tumor growth was delayed and the resulting tumors were quite small. The earliest alteration leading to hepatocellular carcinoma was basophilic hyperplasia, which reflected an increase in free, as well as bound, hepatocytic ribosomes. Hyperplastic nodules were composed of hepatocyte aggregates with characteristics similar to those seen in the earlier stage. The neoplastic nodules and hepatocellular carcinomas were formed by cells containing large, smooth fingerprints (closely packed concentric membranous formations devoid of ribosomes) and free ribosomal aggregates. The protective action of ACTH toward AFB₁ hepatocarcinogenesis may be related to adrenal stimulation, because corticosteroids appear

to affect the binding of polysomes to endoplasmic reticulum membranes. (49 refs.)

- 77-6175 **Acute Toxicity of Aflatoxin B₁ and Rubratoxin B in Dogs.** (Eng) Hayes, A. W. (Dept. Pharmacology and Toxicology, Univ. Mississippi Medical Center, Jackson, MS); Williams, W. L. *J Environ Pathol Toxicol* 1(1): 59-70; 1977.

The effect of ip administered aflatoxin B₁ (AFB₁) and/or rubratoxin B on 14 dogs was determined by serum tests, observations of clinical signs and survival times, and evaluation of gross and microscopic lesions. The dog is sensitive to the toxic effects of both mycotoxins. SGOT, serum lactic dehydrogenase (LDH) and alkaline phosphatase activities, and survival time varied in relation to dose and to the mycotoxin(s) administered. At 24 hr post exposure all three enzymes were elevated regardless of dose with AFB₁ + rubratoxin B except LDH, which was within the normal range but only at the lowest dose level. Several serum constituents, including blood urea nitrogen, cholesterol, uric acid, and total bilirubin, were elevated, but serum glucose was depressed in dogs treated with the multiple-toxin regimen. These changes were not seen in dogs given only AFB₁ but they were characteristic in rubratoxin-treated animals. Gross findings at necropsy were similar in all dogs regardless of the dose regimen. A striking similarity existed between the lesions induced by the mycotoxin combination and those lesions reported for dogs fed toxic feed or occurring in cases of hepatitis X. The severe kidney lesions in dogs exposed to the mycotoxin combination resembled the kidney lesions reported in natural outbreaks of hepatitis X. There can be little doubt of an association between hepatitis X and AFB₁, although the disease probably involves more than a single toxic factor. The results suggest that AFB₁ is the primary etiological factor in canine hepatitis X but that rubratoxin B also may be involved. (22 refs.)

- 77-6176 **Effects of Fungus (*Aspergillus parasiticus*) Toxins on the Chromosomes of Human Lymphocytes In Vitro.** (Eng) Leon-Cazares, J. M. (Laboratorio de Biología Celular, Departamento de Biología Experimental, Instituto de Biología, Universidad Nacional Autónoma de México, México); Aroche-Alfonso, R. M. *Toxicon* 15(6): 489-496; 1977.

Chromosomal damage induced in human lymphocytes by a 72-hr incubation with *Aspergillus parasiticus* strain NRRL 2999 (aflatoxin-producing) was compared with that induced by *A. tamarii* strain NRRL 429 (non-aflatoxin-producing). *A. parasiticus* cultures had a mitotic index of 4.50%, *A. tamarii* cultures, 1.88%. The mitotic damage in the two cultures was 11.3% and 1.7%, respectively; furthermore, about 1000 more mitotic figures were seen in the *A. parasiticus* culture. The distribution of chromosomal damage by class in the *A.*

parasiticus culture was as follows: A, 22.4%; B, 11.2%; C, 41.9%; D, 13.4%; E, 8.3%; F, 0.4%; and G, 2.5%. Damage was more frequent in long arms than in the short arms, and practically no damage was observed in the centromeric region. (29 refs.)

- 77-6177 **Effect of Drying with Hot Forced Draft and Mincing Bracken Fern on its Carcinogenic Activity.** (Eng) Mori, H. (Dept. Pathology, Gifu Univ. Sch. Medicine, 40 Tsukasa-machi, Gifu 500, Japan); Kato, K. Ushimaru, Y.; Kato, T.; Hirono, I. *Gann* 68(4): 517-520 1977.

The comparative carcinogenicity of bracken fern, hot air-dried bracken fern and minced bracken fern in ACI was investigated. Group 1 received unprocessed bracken combined with a basal diet in proportions of 1:2 for 46 days, 1:3 for 70 days and 1:4 for 64 days. Group 2 received bracken fern dehydrated by a 70 to 90 C hot air draft in a 1:2 ratio with basal diet for 130 days. Group 3 received minced bracken fern (paste-like) in a 1:2 ratio with basal diet for 110 days. The animals were autopsied at death or after 480 days. Intestinal tumors were found in 15/18 rats in group 1. There were 24 tumors in the ileum, 1 in the cecum and 1 in the colon. Intestinal tumors were noted in 10/12 group 2 rats. There were 20 ileal tumors and 1 urinary bladder tumor. Intestinal tumors were noted in 13/13 group 3 rats. There were 22 ileal tumors and 2 urinary bladder tumors. The mean number of tumors/rat in the three groups was 5.4, 4.9, and 5.9, respectively. The control group (16 rats) had 1 tumor in the cecum and one breast tumor. Neither mincing nor heating affected the bracken carcinogen. Thus, there may not be an enzyme in the bracken which inhibits carcinogenicity. (8 refs.)

- 77-6178 **Cancer in Cattle Associated with an Environmental Carcinogen and a Papilloma Virus (Meeting Abstract).** (Eng) Jarrett, W. F. (Dept. Veterinary Pathology, Univ. Glasgow Veterinary Sch., Bearsden, Glasgow, G61 1QH, Scotland). In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September 1977*. International Agency for Research on Cancer. (Lyon, France): p. 67; 1977. (no refs.)

- 77-6179 **Frameshift Mutagenicity of Certain Naturally Occurring Phenolic Compounds in the "Salmonella/Microsome" Test: Activation of Anthraquinone and Flavonol Glycosides by Gut Bacterial Enzymes.** (Eng) Brown, J. P. (Dynapol, 1454 Page Mill Road, Palo Alto, CA 94304); Dietrich, P. S.; Brown, R. J. *Biochem Soc Trans* 5(5): 1489-1492; 1977.

Of 26 hydroxylated anthraquinones assayed in the *Salmonella typhimurium*/microsome test, a high percentage exhibited mutagenicity for strains TA1537, TA1538, and TA98, which are particularly sensitive to frameshift mutagens. When tested with gut bacterial enzymes, all anthraquinone glucosides were mutagenic for TA1537, apparently owing to the formation of the free aglycones that are specific for this strain. Frameshift mutagenicity among 14 flavonoid compounds was mainly confined to the flavonols. The mutagenic activity of two quercetin glycones for TA100, TA1537, and TA98 was increased ten- to twentyfold by incorporating gut bacterial enzymes and microsomal enzymes in the assay. (10 refs.)

77-6180 Activation of Monooxygenases in Human Liver by 7,8-Benzoflavone. (Eng) Kapitulnik, J. (Dept. Pharmacology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Poppers, P. J.; Buening, M. K.; Fortner, J. G.; Conney, A. H. *Clin Pharmacol Ther* 22(4): 475-488; 1977.

The addition of 10^{-4} M 7,8-benzoflavone (BF) to homogenates of human liver obtained at autopsy or surgical biopsy increased the rate of benzo(a)pyrene hydroxylation up to 11 fold. At 10^{-4} M, BF also increased the rates of hydroxylation of zoxazolamine and antipyrine, but it inhibited these reactions at 10^{-6} M. The effects of BF on the hydroxylation of benzo(a)pyrene and zoxazolamine in microsomes from human liver were similar to those in homogenates. When added to homogenates of surgical liver biopsy samples, BF had little or no effect on the oxidative metabolism rates of 7-ethoxycoumarin, coumarin, and hexobarbital. Marked differences in the activating and inhibiting effects of BF were observed in different liver samples. These differences may result both from the presence of multiple monooxygenases in varying amounts in the different liver samples and from a selective effect of BF on certain of the monooxygenases. (33 refs.)

77-6181 Evaluation of the Mutagenic Effects of Ethyl Alcohol by Different Techniques. (Eng) Badr, F. M. (Dept. Zoology, Faculty Science, Kuwait Univ., Kuwait, P.O.B. 5969); Badr, R. S.; Asker, R. L.; Hussain, F. H. *Adv Exp Med Biol* 85A: 25-46; 1977.

The mutagenic effects of ethyl alcohol were examined in dominant lethal mutation tests with CBA/Fa Cam mice, micronucleus tests with CBA/J mice, and human lymphocyte culture tests. The first test revealed an induction of dominant lethal mutations in spermatozoa at different stages of development and maturation, the second revealed an increase in the frequency of micronuclei, and the third revealed high incidence of chromosome structural aberrations in the treated cultures. (34 refs.)

77-6182 The Effect of Chronic Alcohol Intake upon the Hepatic Microsomal Carcinogen-Activation System. (Eng) Capel, I. D. (Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey, RH8 OTL, England); Williams, D. C. *IRCS Med Sci: Cancer* 5(9): 448; 1977.

The effect of chronic alcohol administration on the activation and DNA binding of benzo(a)pyrene in the microsomal oxidation system of male TO rats was investigated. Following po and ip administration of ethanol, there was a decrease in BP hydroxylase activity and in DNA binding of BP. Therefore, chronic hepatic damage induced by ethanol should lower the carcinogen-activation potential of the liver. (7 refs.)

77-6183 Prognostic Effect of Tobacco and Alcohol Use in Patients with Oral Tongue Cancer. (Eng) Johnston, W. D. (Ellis Fischel State Cancer Hosp., Business 70 & Garth Ave., Columbia, MO 65201); Ballantyne, A. J. *Am J Surg* 134(4): 444-447; 1977.

Of 351 patients with oral tongue cancer, 96/308 chronic users of tobacco and/or alcohol were dead from their tumor within 5 yr, compared with only 6/43 nonusers. In addition, nonusers were older than the users when they developed the disease. Second primary cancers developed in 27.4% of the users but in only 18.5% of the nonusers. (6 refs.)

77-6184 Tumorigenic Agents in Unburned Processed Tobacco: N-Nitrosodiethanolamine and 1,1-Dimethylhydrazine. (Eng) Schmeltz, I. (Div. of Environmental Carcinogenesis, Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, New York 10595, U.S.A.); Abidi, S.; Hoffmann, D. *Cancer Lett (Amsterdam)* 2(3): 125-132; 1977.

The identification and quantification of two tumorigenic agents, N-nitrosodiethanolamine and 1,1-dimethylhydrazine, in burned tobacco were reported. N-Nitrosodiethanolamine was detected by the isotope dilution technique at levels ranging from 0.1 ppb in flue-cured tobacco not treated with the herbicide maleic hydrazide (MH-30) to 173 ppb in Burley tobacco which had been treated with MH-30 prior to harvesting. Diethanolamine in the herbicide is thought to be the source of N-nitrosodiethanolamine; cautious use of chemicals on crops destined for man is advocated. 1,1-Dimethylhydrazine, a tumorigenic agent in mice, was isolated by electron-capture gas chromatography from various types of tobacco in amounts ranging from 0 to 147 nanograms/g tobacco. The origin of 1,1-dimethylhydrazine is unknown, but it is believed to arise from bacterial or enzymic processes that occur during curing. Further studies will be

done on the possible presence of these carcinogens in tobacco smoke, as well as in unburned tobacco. (15 refs.)

- 77-6185 **Determination of N-Nitrosornicotine in Tobacco by Gas Chromatography/Mass Spectroscopy.** (Eng) Munson, J. W. (Coll. Pharmacy, Univ. Kentucky, Lexington, KY 40506); Abdine, H. *Anal Lett* 10(10): 777-786; 1977.

The amount of N-nitrosornicotine in 2 g samples of various tobaccos was determined by gas chromatography and mass spectroscopy. In cigarettes, the values ranged from 0.8 to 3.4 ppm; in chewing tobacco from 1.0 to 26.4 ppm; in cigars, from 1.7 to 2.7 ppm; in pipe tobacco, from 1.6 to 3.1 ppm; and in snuff, from 3.2 to 9.3 ppm. (5 refs.)

- 77-6186 **An Investigation of the Biological Activity of Tobacco and Cytrel Condensate by the Mouse Epidermal Hyperplasia Test.** (Eng) Fawell, J. K. (Inveresk Res. International, Inveresk Gate, Musselburgh, Scotland); Clark, D. G. *Proc Eur Soc Toxicol* 18: 222-224; 1977.

The smoke condensate from cigarettes containing Cytrel, a cellulose-based tobacco supplement, produced less epidermal hyperplasia in Charles River CD-1 mice than the smoke condensate from cigarettes containing tobacco only. This was demonstrated at both high (140 mg) and low (99 mg) doses of each of the topically applied condensates. Because the mouse epidermal test is an index of potential carcinogenicity, this result suggests that inclusion of Cytrel in cigarettes may reduce their carcinogenic activity. (4 refs.)

- 77-6187 **The Comparative 'In Vitro' Toxicity of Tobacco and the Tobacco-Supplement, Cytrel.** (Eng) Bensilum, S. (Life Science Res., Stock, Essex, England); Daniel, J. W. *Proc Eur Soc Toxicol* 18: 273-274; 1977.

The biological effects of cigarettes containing tobacco and either 0%, 20%, 50%, or 100% Cytrel on rat trachea, rabbit alveolar macrophages, and the mucociliary activity of rabbit trachea were investigated. In all three systems, the response to Cytrel was less than that of tobacco. The addition of Cytrel to tobacco resulted in a progressive and significant reduction in all activity except ciliary activity. (4 refs.)

- 77-6188 **Scanning Electron Microscope Observations of the Rat Larynx.** (Eng) Smith, G. (Group Res. and Development Centre, British-American Tobacco Co. Ltd., Southampton, Hants, England). *Proc Eur Soc Toxicol* 18: 279-281; 1977.

Scanning electron microscopy was used to study the larynx of SPF white rats exposed to cigarette smoke (2 10-min exposures/day for 6 wk) from a system giving 1 volume of whole smoke mixed with 12 volumes of air. The epiglottis of the exposed animals was usually unchanged, but squamous metaplasia occurred on the ventral and lateral surfaces of the larynx anterior to the vocal cords. This metaplasia was complete except for the ventral depression and a narrow band anterior to the ventral ridge. Posterior to the ventral ridge the nonciliated columnar epithelium either persisted or became squamous. On the medial aspect of the vocal cords the band of squamous cells increased in area due to the metaplasia. (2 refs.)

- 77-6189 **Pathological Alterations in Syrian Golden Hamster Lungs after Passive Exposure to Cigarette Smoke.** (Eng) Ketkar, M. B. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, 3000 Hannover 61, W. Germany); Reznik, G.; Mohr, U. *Toxicology* 7(3): 265-273; 1977.

Pathological alterations in the lungs of Syrian golden hamsters after 1 yr of passive inhalation of the smoke of two research cigarettes differing in their total smoke delivery and condensate were examined. The animals were exposed to the cigarette smoke daily 5 days/wk for 52 wk. Experimental and control animals were killed 1 day after termination of exposure. Focal hyperplasia was observed in the larynx of 7/10 smoke-exposed animals and in the trachea of 4/5. Twenty-four of the exposed animals demonstrated slight round-cell infiltration of the laryngeal and tracheal submucosa and lungs. Histological examination of lung tissue showed chronic pathological alterations. One papilloma of a lobar bronchus and seven pulmonary adenomas were found. Dark-brown patches (2-3 mm in diameter) composed of clumps of cells containing pale to dark-brown pigment (Brown cells) and giving an intense, positive staining reaction for iron were common on the lung surface. Qualitative and quantitative differences existed between the two cigarette groups with respect to the occurrence of these Brown cell clumps. Ultrastructural examination showed that the clumps were alveolar macrophages, the cytoplasm of which was crowded with phagocytosed material of high electron density. Nearly all smoke-exposed animals demonstrated perivascular inflammatory cells in the liver, varying degrees of amyloidosis of the liver and kidney tissue were also seen. The response of the lung tissue to smoke exposure appears to depend upon the amount of mainstream total particulate matter, the amount of condensate, the time exposed, and the number of cigarettes. (21 refs.)

- 77-6190 **Comparative Inhalation Toxicity of Smoke from Cigarettes During a Six-Week Study** (Eng) Wilton, L. V. (Group Res. and Development Centre

British-American Tobacco Co. Ltd., Southampton, Hants., England); Binns, R. *Proc Eur Soc Toxicol* 18: 270-272; 1977.

Male and female rats were exposed to the smoke of cigarettes modified to deliver a range of total particulate matter (TPM). The animals were exposed during a 5-day acclimatization period plus 42 consecutive days of two exposures/day. Significant amounts of smoke were inhaled, and the largest proportion of TPM (250-500 $\mu\text{g/g}$ tissue) was retained in the lung. Following acclimatization, breathing patterns and blood carboxyhemoglobin levels remained steady. These physiological indicators, together with dosimetry data, imply that the exposure conditions did allow the effective dosing of animals, as necessary for short-term bioassays of smoke. (3 refs.)

77-6191 **The Effect of Exposure Conditions on Cigarette Smoke Deposition in the Respiratory System of Male Rats.** (Eng) Binns, R. (Group Res. and Development Centre, British-American Tobacco Co. Ltd., Southampton, Hants, England); Lugton, W. G.; Dyas, B. J. *Proc Eur Soc Toxicol* 18: 267-269; 1977.

Cigarette smoke deposition in the respiratory system of male Wistar rats under various exposure conditions was investigated. There was a high penetration of smoke into the lower respiratory system with every concentration; there was a small effect of concentration on distribution. Intermittent exposure resulted in a lower deposition than continuous exposure. Nonacclimatized animals retained twice as much as acclimatized ones, mainly in the head. (4 refs.)

77-6192 **Cigarette Smoking and Human Pulmonary Macrophages.** (Eng) Martin, R. R. (Baylor Coll. Medicine, Houston, TX); Warr, G. A. *Hosp Pract* 12(9): 97-104; 1977.

The effects of cigarette smoking on pulmonary alveolar macrophages (PAM) were studied in > 400 normal subjects using cells obtained by saline pulmonary lavage. Cells from young (av age, 25 yr) asymptomatic cigarette smokers were compared with those from a comparable nonsmoking population. Light or electron transmission microscopy showed that PAM from cigarette smokers contained large amounts of cytoplasmic inclusions and displayed an altered surface morphology. PAM from smokers were agglutinated by concanavalin-A, but those from nonsmokers were not. PAM from cigarette smokers were less able to phagocytose staphylococci than macrophages from nonsmokers, but phagocytosis of *Candida krusei* was similar with cells from both groups. Migration of PAM was increased with cells from cigarette smokers. These macrophages, however, were not responsive to the migration inhibitory factor. Aryl hydrocarbon hydroxylase was induced to high levels in the PAM

from cigarette smokers. Cigarette smoking impaired the ability of PAM to mediate several of the macrophage-dependent in vitro lymphoproliferative responses, which may indicate a local defect in cell-mediated immunity in the lung associated with smoking. (no refs.)

77-6193 **Induction of Aryl Hydrocarbon Hydroxylase in Human Pulmonary Alveolar Macrophages and Peripheral Lymphocytes by Cigarette Tars.** (Eng) McLe-more, T. L. (Department of Medicine, Baylor College of Medicine, 1200 Moursund Avenue, Houston, Texas 77030 U.S.A.); Warr, G. A.; Martin, R. R. *Cancer Lett (Amsterdam)* 2: 161-168; 1977.

The in vitro induction of aryl hydrocarbon hydroxylase (AHH) in human pulmonary alveolar macrophages (PAMs) and peripheral lymphocytes from both smokers and non-smokers by pigment obtained from PAMs of smokers (1 mg) or by extracts of cigarette tar (28 μg) was examined. When challenged with approx 0.2 mg of pigment extracts from lysed PAMs of smokers and from cigarette tar extracts, non-pigmented PAMs from non-smokers were able to ingest and accumulate the pigment. Fluorimetric determinations showed that pigment from smokers' PAMs did not induce enzymic activity in either PAMs or lymphocytes, while cigarette tar significantly induced AHH activity in both PAMs and lymphocytes. These results substantiate previous reports that cigarette tars induce AHH activity in PAMs and lymphocytes of cigarette smokers. (15 refs.)

77-6194 **A Comparison of the Effects of 3-Methylcholanthrene and Tobacco Smoke on the Induction of Aryl Hydrocarbon Hydroxylase in Female Wistar Rats and Syrian Golden Hamsters.** (Eng) Fergie, R. C. (Dept. Drug Metabolism and Biochemistry, Hazleton Labs. Europe Ltd., Harrogate, Yorks., England); Turner, D. M. *Proc Eur Soc Toxicol* 18: 203-205; 1977.

The effects of 3-methylcholanthrene (3-MC, 4 daily ip injections) and tobacco smoke on the induction of aryl hydrocarbon hydroxylase (AHH) in lung and liver microsomes from Wistar rats and Syrian golden hamsters were investigated. 3-MC significantly increased AHH activity in both rat tissues, but only in the hamster liver. Smoke-induced changes in the rat liver and lung were not as pronounced as those induced by 3-MC. Although AHH activities in the hamster liver and lung were higher than those after 3-MC treatment, smoke had no significant effect on this activity in either tissue. Endogenous AHH levels were 10 times higher in hamster lung and liver microsomes than in those of the rat. In light of these results, the relationship between AHH inducibility and susceptibility to chemical carcinogenesis remains unclear. (5 refs.)

- 77-6195 **Biologic Analysis of Fetal MRC Rat Lung Epithelial Cells Treated with 3-Methylcholanthrene in Culture: Premalignant and Malignant Stages.** (Eng) Indo, K. (Dept. Pathology, Hyogo Medical Coll., Mukogawa-cho, Nishinomiya, Hyogo, Japan). *J Natl Cancer Inst* 58(2): 351-360; 1977.

Fetal MRC rat lung primary cell sheets, in which reconstruction of bronchial tissue occurred, were treated with 3-methylcholanthrene (3-MC) to examine its effect on lung epithelial elements. Cloned lines were established by subculturing of epithelial outgrowths from primary cell sheets induced by 3-MC. Newborn MRC rats were inoculated sc with these cells. During the initial culture stages, the 3-MC treated cells temporarily formed benign epithelial structures in the scar tissue that developed from the injection and then regressed. These structures could be roughly divided into tubular, squamous, and undifferentiated stratified epithelium. After being subcultured several times, six of the cell lines induced malignant tumors in animals within 1-5 mo after inoculation. Those cell lines that produced benign squamous epithelium in scars tended toward lamellar keratinization in vitro. Malignantly transformed cell lines showed piled-up areas. Two of the five lines that formed squamous cell carcinomas in animals showed keratinization that occurred inside the piled-up areas. Single-cell keratinization and loss of regularity in keratinization were also observed. These alterations signify qualitative changes in the in vitro keratinization, which may reflect the biologic behavior of cells during premalignant and malignant stages. These findings may confirm the existence of steps in the development of malignant tumors from normal rat bronchial epithelium. (14 refs.)

- 77-6196 **Immunosuppressive Effects of 3-Methylcholanthrene Given Intratracheally in Various Inbred Strains of Mice.** (Eng) Levy, R. L. (508 Van Dyke Ave., Del Mar, CA 92014); Barrington, M. H.; Lerner, R. A.; Griffin, G. F.; Whitmire, C. E. *Cancer Res* 37(11): 3892-3894; 1977.

The immunosuppressive effects of 500 μ g of 3-methylcholanthrene (3-MC) administered intratracheally C3Hf/Mai, C57BL/6, or DBA/2J mice was investigated. The immune response to goat RBC was markedly suppressed by 3-MC on day 19 in C3Hf/Mai mice and on all days except day 21 in C57BL/6 mice. Immunodepression was not observed with DBA/2 mice. There was no significant difference between the immune response of male and female mice in any of these strains. Thus, systemic immunosuppression cannot be discounted as a contributing factor in permitting tumor growth. In this manner, a transformed cell could escape detection by the immune system and develop into a tumor. (12 refs.)

- 77-6197 **Geldanamycin Inhibition of 3-Methylcholanthrene-Induced Rat Embryo Cell**

Transformation. (Eng.) Price, P. J. (Microbiological Assoc., Torrey Pines Res. Center, LaJolla, CA 92037); Suk, W. A.; Skeen, P. C.; Spahn, G. J.; Chirigos, M. A. *Proc Soc Exp Biol Med* 155(4): 461-463; 1977.

In Fischer rat embryo cells in vitro, nontoxic levels (0.3 or 1.0 μ g/ml) of geldanamycin inhibited the induction of endogenous rat leukemia virus by 5-iodo-2'-deoxyuridine and protected cells from transformation by 3-methylcholanthrene. (11 refs.)

- 77-6198 **Homogenates of Pregnant Rat and Fetal Tissues Metabolize Carcinogens to Mutagens Detected by *Salmonella typhimurium* TA98 and TA100.** (Eng) Sehgal, C. B. (Dept. Botany, Univ. Delhi, Delhi 110007, India); Hut-ton, J. J. *Mutat Res* 46(5): 325-344; 1977.

Homogenates of placenta, liver, lung, intestine, and skin from pregnant rats and their 20-day-old fetuses were compared for their ability to metabolize chemicals to mutagens. Pregnant females were either untreated or received phenobarbital, 3-methylcholanthrene (3-MC) or polychlorinated biphenyls to induce drug-metabolizing enzymes. 2-Aminoanthracene (AA), benzo(a)pyrene (BP), 3-MC, 7,12-dimethylbenz-(a)anthracene (DMBA) and the Swain fraction 5 of cigarette smoke condensate were used as the test substances, and *Salmonella typhimurium* TA98 and TA100 were used as indicators of mutagen formation. TA98 was more efficiently mutagenized by metabolites of AA and Swain fraction 5, and TA100 by metabolites of BP, 3-MC, and DMBA. Polychlorinated biphenyls and 3-MC were very good inducers of aryl hydrocarbon hydroxylase activity in the mother and fetus. Generally, maternal and fetal tissue homogenates from organs of animals treated with polychlorinated biphenyls or 3-MC were better metabolizers of test compounds than homogenates from PB-treated or untreated animals. There was an optimal balance between amount of tissue homogenate and concentration of test compound for max yield of revertants. Among the organs tested, maternal and fetal liver were the best sources of enzymes metabolizing the test substances. However, the activity of fetal liver was much lower than maternal liver. (27 refs.)

- 77-6199 **Mutagenic Activity of Airborne Particulate Organic Pollutants.** (Eng) Pitts, J. N. (Statewide Air Pollution Res. Center, Univ. California, Riverside, CA 92521); Grosjean, D.; Mischke, T. M.; Simmon, V. F.; Poole, D. *Toxicol Lett* 1(2): 65-70; 1977.

The Ames' *Salmonella typhimurium* assay was used to test for mutagenic activity in nine air samples obtained at one rural site (Camp Paivika in the San Bernardino Mountains) and eight urban sites (Anaheim, Banning, Lennox, Los Angeles, Los Alamitos, Pasadena, Pomona and Riverside) in California. Each sample was tested twice at at least six doses

(0.1, 0.5, 1, 5, 10 and 50 μ liters) on five histidine-dependent strains of *Salmonella* (TA98, TA100, TA1535, TA1537, and TA1538). The samples collected at Camp Paivika were inactive in spite of appreciable organic content. All samples collected at the remaining urban sites demonstrated mutagenic activity without metabolic activation. For the four highest doses, the dose response curves were linear. Assays of some of the samples at the two smallest doses did not result in a significant increase in the number of *his* + revertants above the background level. For all but one urban sample demonstrating a slight increase, the addition of the metabolic activation system did not increase the observed mutagenic activity. Since most polycyclic hydrocarbons are not active in the absence of metabolic activation in the Ames assay, it is suggested that oxygenation of polycyclic hydrocarbons by photochemical smog produces products not requiring metabolic activation. (23 refs.)

77-6200 Carcinogenic Hydrocarbons and the Incidence of Cancer Mortality among Residents Near an Automobile Highway. (Ger.) Blumer, W. (FMH Allgemeine Medizin, CH-8754 Netstal/G1.); Blumer, M.; Reich, T. *Fortschr Med* 95(23): 1497-1498, 1551-1552; 1977.

The carcinogenic effects of hydrocarbons on the incidence of death due to cancer for people living along a highway frequented by 4,000-5,000 vehicles daily are discussed. It had been shown previously that, over a 12-yr period, cancer mortality was nine times higher for 232 people living along a highway than for those living in a traffic-free area. Soil analyses indicated that high concentrations of mostly unsubstituted polycyclic hydrocarbons, such as phenanthrene and other aromatic ring systems of seven and eight members, were present along the edge of the highway. Specific carcinogens found included pyrene, anthracene, and methylchrysene. In a traffic-free area, the soil content of these compounds was 12 times less and in the Alps, with no cars over a wide area, it was 50 times less. Chemical analysis showed that these hydrocarbons come from fuel combustion. The highest hydrocarbon value reported was 296 mg/kg/dry soil along a road on the outskirts of a village; the lowest value, 4 mg/kg, was from an alpine meadow 1,600 m above sea level and 1 km from a highway. (26 refs.)

77-6201 A Comparative Analysis of the Electrostatic Potentials of Some Polycyclic Aromatic Hydrocarbons. (Eng) Politzer, P. (Dept. Chemistry, Univ. New Orleans, New Orleans, LA 70122); Daiker, K. C. *Int J Quantum Chem Quantum Biol Symp* (4): 317-325; 1977.

Electrostatic potential maps for benzo(a)pyrene, 5-methylchrysene, and 12-methylbenz(a)anthracene are presented and compared. The maps imply that chrysene, a weak carcinogen, becomes as potent as benzo(a)pyrene upon sub-

stitution of a methyl group at position 5. A key factor in hydrocarbon carcinogenicity may be the presence of two regions of significant negative potential on opposite sides of the molecule, suitably located with respect to each other. (21 refs.)

77-6202 High Mutagenicity of Metabolically Activated Chrysene 1,2 Dihydrodiol: Evidence for Bay Region Activation of Chrysene. (Eng) Wood, A. W. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ 07110); Levin, W.; Ryan, D.; Thomas, P. E.; Yagi, H.; Mah, H. D.; Thakker, D. R.; Jerina, D. M.; Conney, A. H. *Biochem Biophys Res Commun* 78(3): 847-854; 1977.

Chrysene and its three metabolically possible vicinal trans-dihydrodiols were tested for mutagenicity towards *Salmonella typhimurium* strain TA100 in the presence of hepatic microsomes or a highly purified hepatic microsomal monooxygenase system. The products formed during the metabolic activation of chrysene 1,2-dihydrodiol were > 20 times as mutagenic as the metabolites formed from chrysene, chrysene 3,4-dihydrodiol or chrysene 5,6-dihydrodiol. When the double bond in the 3,4-position of chrysene 1,2-dihydrodiol was saturated, the resulting tetrahydrodiol could not be metabolically activated. These results, which strongly suggest that chrysene 1,2-dihydrodiol is activated by metabolism to either or both of the diastereomeric chrysene 1,2-diol-3,4-epoxides, provide additional support for the bay region theory of polycyclic hydrocarbon carcinogenicity. (32 refs.)

77-6203 Hyperplastic Alveolar Nodules of the Rat Mammary Gland: Tumor-producing Capability In Vivo and In Vitro. (Eng) Sinha, D. (Dept. of Breast Surgery and Breast Cancer Res. Unit, Roswell Park Memorial Inst., New York State Dept. of Health, Buffalo, New York, 14263, U.S.A.); Dao, T. L. *Cancer Lett (Amsterdam)* 2: 153-160; 1977.

The tumor-producing capability of 7,12-dimethylbenz(a)anthracene (DMBA)-induced hyperplastic alveolar nodules of the rat mammary gland in vivo and in vitro was determined. DMBA (5 mg, iv) administered to female Wistar-Furth rats provided donors of hyperplastic alveolar nodules. Isologous recipient rats received four nodules each. A single dose of varying concentrations of DMBA (0.5, 1.5, 3.0, g/100 g body wt, iv) was given 10 days later. In vitro, the nodules were exposed to DMBA (1 μ g/ml x 2, 1 μ g/ml, and 0.1 μ g/ml) in the culture medium containing hormone supplements (insulin, 0.5 μ g/ml; prolactin, 5 μ g/ml; estradiol-17 β , 0.001 μ g/ml; progesterone, 0.1 μ g/ml) for either 3 or 6 days. After 9 days in culture, the nodules were transplanted to recipient rats. Examination of host mammary glands and grafts after 90 days revealed no significant in-

crease in tumor production; instead the hyperplastic alveolar transplants developed into ductal or lobulo-alveolar outgrowths. It is concluded that carcinogen-induced hyperplastic alveolar nodules were not preneoplastic lesions in mammary carcinogenesis in the rat. (10 refs.)

- 77-6204 Metabolism of Benzo(a)pyrene with Isolated Hepatocytes and the Formation and Degradation of DNA-binding Derivatives.** (Eng) Burke, M. D. (Dept. Biochemistry, Univ. Surrey, Guildford, Surrey, GU2 5XH, England); Vadi, H.; Jernstrom, B.; Orrenius, S. *J Biol Chem* 252(18): 6424-6431; 1977.

The metabolism of ^{14}C -benzo(a)pyrene (BP) with isolated hepatocytes from 3-methylcholanthrene-treated rats was examined by high-pressure liquid chromatography, along with covalent binding of ^3H -BP metabolites to intracellular DNA. The effects of α -naphthoflavone, salicylamide, trichloropropene oxide, and diethylmaleate, individually or combined, on the metabolism and covalent DNA binding of BP were determined. The initial organic-soluble metabolites were arene oxides, phenols, quinones, and dihydrodiols that were subsequently converted to relatively polar, organic-soluble nonconjugated and sulfate-conjugated metabolites and to aqueous-soluble nonconjugated and glucuronide- and glutathione-conjugated metabolites. α -Naphthoflavone inhibited the formation of BP metabolites that covalently bound to hepatocyte DNA but the binding was stimulated by salicylamide, trichloropropene oxide, or diethylmaleate. These results indicate that BP oxide hydration and glutathione conjugation, and glucuronide and sulfate conjugation of hydroxylated metabolites operate in concert to detoxify electrophilic DNA-binding BP metabolites in the hepatocytes. Thus, the degree of covalent binding of BP to the nuclear DNA of isolated hepatocytes is apparently correlated with the production of electrophilic BP metabolites and the rate of their disposal by epoxide hydratase and conjugation reactions. (65 refs.)

- 77-6205 Induction of Benzo(a)pyrene Metabolites by Liver Microsomes from Lindane Treated Rats (Meeting Abstract).** (Eng) Decloitre, F. (Institut de Recherches Scientifiques sur le Cancer, B.P. No 8, 94800 Villejuif, France); Mikol, Y. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 69; 1977. (no refs.)

- 77-6206 Ellipticines as Inhibitors of Microsomal Hydroxylases. Protective Effects Against Mutagenicity and Carcinogenicity (Meeting Abstract).** (Eng) Lesca, P. (Laboratoire de Pharmacologie et de Toxicologie

fondamentales du CNRS, Toulouse, France); Lecoite, P.; Paoletti, C. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 85; 1977. (no refs.)

- 77-6207 Continuous Spectrofluorimetric Assay of Epoxide Hydrase (Meeting Abstract).** (Eng) Dansette, P. M. (Institut de Biochimie, Orsay, France); Jerina, D. M. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 84; 1977. (no refs.)

- 77-6208 Mechanism of Phage ϕX174 DNA Inactivation by Benzo(a)pyrene-7,8-dihydrodiol-9,10-epoxide.** (Eng.) Hsu, W. T. (Franklin McLean Memorial Res. Inst., Univ. Chicago, Chicago, IL 60637); Lin, E. J.; Harvey, R. G.; Weiss, S. B. *Proc Natl Acad Sci USA* 74(8): 3335-3339; 1977.

The relationship between the extent of (\pm)-trans-7,8-dihydroxy -anti- 9,10-epoxy-7,8,9,10- tetrahydrobenzo(a)pyrene (BP diolepoxide) binding to ϕX174 DNA and its effect on infectivity was investigated. The results suggest that one molecule of bound diolepoxide is sufficient to block the replication of a single molecule of ϕX174 DNA. Sedimentation analysis of BP-modified ϕXDNA indicates homogeneity in size and a sedimentation rate close to that of unmodified viral DNA. The rate of DNA synthesis is lowered when BP- ϕXDNA serves as a template; the total amount of DNA polymerized is also reduced. Also, the propagation of synthetic DNA strands is blocked, so that incomplete complementary chains are assembled. The relationship of these results to the mutagenicity and carcinogenicity of BP diolepoxide is discussed. (27 refs.)

- 77-6209 Differences in Mutagenicity of the Optical Enantiomers of the Diastereomeric Benzo(a)pyrene 7,8-Diol-9,10-epoxides.** (Eng) Wood, A. W. (Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche Incorporated Nutley, NJ 07110); Chang, R. L.; Levin, W.; Yagi, H.; Thakker, D. R.; Jerina, D. M.; Conney, A. H. *Biochem Biophys Res Commun* 77(4): 1389-1396; 1977.

The mutagenicity of the optical enantiomers of the diastereometric benzo(a)pyrene (BP) 7,8-diol-9,10-epoxides was tested in *Salmonella typhimurium* strains TA98 and TA100 and in V79 Chinese hamster cells. In TA98 and TA100, (-)-7 β ,8 α -dihydroxy-9 β ,10 β -epoxy-7,8,9,10- tetrahydro-BP induced from 1.3 to 9.5 times as many mutations as the three other optically active stereoisomers. In

Chinese hamster cells, (+)-7 β ,8 α -dihydroxy-9 α ,10 α -epoxy-7,8,9,10-tetrahydro-BP [(-)-diol epoxide-2] induced 6-18 times as many variant colonies. These results are of considerable interest in light of the stereoselective metabolism of BP. The potent mutagenicity of (+)-diol epoxide-2 in mammalian cells, its binding to mouse skin RNA *in vivo*, and the high tumorigenicity of the (-)-BP 7,8-dihydrodiol from which it is derived provide direct evidence that this enantiomer may be the ultimate carcinogenic metabolite of BP. (26 refs.)

77-6210 Changes in the Content of Total Lipids, Phospholipids, and Neutral Lipids in Rat Liver Mitochondria and Mitochondria under Chemical Carcinogenesis. (Rus.) Poliakov, V. M. (Rostov Res. Inst. Oncology, Ministry Public Health USSR, Moscow, USSR); Lankin, V. Z.; Arkhangelskaia, A. V.; Blagorodov, S. G. *Bio-khimiya* 42(3): 499-504; 1977.

A sharp increase in total lipids and neutral lipids and a marked decrease in phospholipids were observed in mitochondria and mitochondria from the livers of rats bearing sarcomas induced by a single injection of 3,4-benzopyrene (5 mg). Anthracene, a noncarcinogenic hydrocarbon, did not affect the composition of rat liver subcellular particles. Thus, disturbances in the functions of subcellular particles during carcinogenesis are due to marked changes in the chemical composition of the biomembranes. The data support the hypothesis of lipid mobilization during tumor growth. (15 refs.)

77-6211 Effect of Dose and Solvent in Benzo(a)pyrene Induced Respiratory Tract Carcinogenesis in Syrian Golden Hamsters (Meeting Abstract). (Eng) Ketkar, M. B. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, W. Germany). In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 78; 1977. (no refs.)

77-6212 Effect of Various Chemicals on the Metabolism of Benzo(a)pyrene by Cultured Rat Colon. (Eng) Autrup, H. (Human Tissue Studies Section, Experimental Pathology Branch, Carcinogenesis Program, Div. Cancer Cause and Prevention, NCI, Bethesda, MD 20014); Harris, C. C.; Fugaro, S.; Selkirk, J. K. *Chem Biol Interact* 18(3): 337-347; 1977.

The effect of various co- and anticarcinogens of colon carcinogenesis in cultured Charles River CD male rat colon incubated with 1.5 μ M benzo(a)pyrene (BP) was determined. The metabolism of labeled BP by various segments of the colon showed that binding to DNA was highest in the de-

scending colon, followed by the rectum and the transverse and ascending colon. Aryl hydrocarbon hydroxylase (AHH) activity was highest in the rectum, followed by the descending, ascending, and transverse colon. Pretreatment of the explants with 5 μ g/ml of benzo(a)anthracene or 20 μ g/ml of phenobarbital had no significant effect on the binding of BP to DNA or on AHH activity; phenobarbital, however, increased BP binding to protein. The metabolites of BP, in decreasing order of occurrence, were quinones, unidentified compounds, 9,10-diol and 7/8,9-triol, tetrols, 7,8-diol, 9-OH BP, and 3-OH BP. BP binding to DNA and protein was lowered by incubation with 3.6 and 18.0 μ M 7,8-benzoflavone and 100 μ M disulfiram. Both compounds also inhibited AHH activity. Exclusion of β -retinyl acetate resulted in lower binding levels and reduced AHH activity. Taurodeoxycholic acid significantly enhanced BP binding to DNA. (51 refs.)

77-6213 Lack of Effect of Trichloropropene Oxide on Benzo(a)pyrene Tumor-initiating Activity on Mouse Skin (Meeting Abstract). (Eng) Alexandrov, K. (Institut de Recherches Scientifiques sur le Cancer, 94 800-Villejuif, France); Dansette, P. M.; Flodrops, M.; Frayssinet, C. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 80; 1977. (no refs.)

77-6214 Effects of Exposure to Acrolein Vapor in Hamsters Simultaneously Treated with Benzo(a)pyrene or Diethylnitrosamine. (Eng) Feron, V. J. (Central Inst. Nutrition and Food Res. TNO, Post Office Box 360, Zeist, Netherlands); Kruijsse, A. *J Toxicol Environ Health* 3(3): 379-394; 1977.

Syrian golden hamsters were exposed repeatedly to acrolein ($\text{CH}_2=\text{CHCHO}$) vapor combined with intratracheal instillation of benzo(a)pyrene (BP) or sc injection of diethylnitrosamine (DNA) for 81 wk. The hamsters, 252 males and 252 females, were evenly distributed between two inhalation chambers, one for air exposure and the other for exposure to 4.0 ppm (9.2 mg/m³) acrolein, 7 hr/day, 5 days/wk, for 52 wk. Equal numbers of animals in each chamber were treated with BP, DNA, or 0.9% NaCl solution. Observations were made of general appearance, body wt, mortality, hematological and biochemical factors, organ wts, and gross and microscopic pathology. At the end of 52 wk, six animals of each sex per chamber not treated with BP or DNA were killed and examined extensively. The remaining hamsters were killed after 81 wk and examined only for changes in the respiratory tract. Exposure to acrolein resulted in abnormal behavior; growth retardation; increases in Hb content, packed cell volume, and relative lung wt; decreased relative liver wt; and rhinitis accompanied by hyper- and metaplasia

of the nasal cavity epithelium. There was no indication of a carcinogenic effect of acrolein. Respiratory tract tumors were found in hamsters of both sexes treated with BP or DENA. The tumor types were those usually seen in hamsters following administration of these carcinogens. Indications of an enhancing effect of acrolein on BP carcinogenesis were doubtful. The carcinogenic effect of DENA on the respiratory tract did not appear to be influenced by exposure to acrolein. It is concluded that acrolein is not an evident cofactor in respiratory tract carcinogenesis. (27 refs.)

- 77-6215 Effects of Localized Chemical Carcinogenesis and Immunosuppression upon Bronchial Preneoplasia in the Dog.** (Eng) Benfield, J. R. (1000 W. Carson St., Torrance, CA 90509); Shors, E. C.; Okita, M.; Matsumura, K.; Cohen, A. H. *J Thorac Cardiovasc Surg* 74(5): 752-760; 1977.

To permit serial observations during the preneoplastic stages of lung carcinogenesis, bronchoscopy was used to expose 54 dogs recurrently to carcinogens at the orifice of the right accessory (intermediate) lobe bronchus. Benzo(a)pyrene (BP) and N-methyl-N-nitrosourea (NMU), either alone or sequentially, were injected into the bronchial submucosa or topically applied to the mucosa in three groups of mongrels and two groups of beagles. Long-term immunosuppression with azathioprine and methylprednisolone was used in one group of beagles. Weekly injections of 45 mg NMU were excessively toxic. However, weekly submucosal injections of up to 45 mg BP and topical application of 5 mg NMU were well-tolerated. The gross bronchoscopic and histologic changes induced by these carcinogens singly or in sequence were similar. Marked mucosal irregularity and stenosis were routinely noted at 3 mo. Serial monthly biopsies of the sites of carcinogen exposure regularly revealed columnar hyperplasia within 1 mo. Squamous metaplasia occurred as early as 4 wk after the first chemical exposure, and it became a persistent and progressive feature by 3 mo. Recurrent atypia with increased mitotic activity was seen, and 76% of all dogs had squamous metaplasia with atypia. Chronic immunosuppression did not alter the pattern of gross and histologic changes. Recurrent trauma alone did not cause squamous metaplasia or any other preneoplastic change. The sequential use of BP-NMU provides a predictable, reproducible means of producing localized endobronchial preneoplasia in the dog. (17 refs.)

- 77-6216 The Influence of Trace Elements on the Hydroxylation of Benzo(a)pyrene.** (Fre) Calop, J. (Pharmacie Centrale C.H.R.G., 38700 La Tronche, France); Burckhart, M. F.; Fontanges, R. *Eur J Toxicol* 9(5): 271-286; 1977.

In vitro cultures of female Swiss mouse liver were used to

study the effects of trace elements on the hydroxylation of benzo(a)pyrene. The mice received 2 mg/100 g body wt 20-methylcholanthrene; 2 days later, they were sacrificed and the livers isolated. Trace elements were tested in concentrations ranging from 0.01 to 100 ppm. The inhibitors of aryl hydrocarbon hydroxylase (AHH) and the respective concentrations required for inhibition were as follows: Zn > 20 ppm, Cu > 20 ppm, Ni > 50 ppm, Cr³⁺ > 5 ppm, V > 20 ppm, Mn > 20 ppm and Cd > 20 ppm. Elements that had little or no effect were Sn, Si, As, Cr⁶⁺ and Ca; in addition, Ni, Cr³⁺ and V were considered neutral at concentrations below the inhibiting level stated above. Zn was an AHH activator at concentrations between 2 and 20 ppm, Al activated above 5 ppm, Cu between 0.3 and 20 ppm, Pb between 5 and 20 ppm, Mn between 0.5 and 20 ppm and Cd between 0.1 and 20 ppm. Mo, Fe³⁺ and Be were inhibitors at all concentrations tested, and Mg and Co were activators at all concentrations. (36 refs.)

- 77-6217 Metal Mutagens and Carcinogens Affect RNA Synthesis Rates in a Distinct Manner.** (Eng) Hoffman, D. J. (Health Effects Res. Lab., Environmental Res. Center, Environmental Protection Agency, Cincinnati, OH 45268); Niyogi, S. K. *Science* 198(4316): 513-514; 1977.

Five mutagenic or carcinogenic metal salts (Pb, Cd, Co, Cu, and Mn), which decrease the fidelity of DNA synthesis in vitro, stimulated chain initiation of RNA synthesis at concentrations that inhibited overall RNA synthesis. In contrast, other metal salts (Zn, Mg, Li, Na, and K) not in this category inhibited chain initiation of RNA synthesis at concentrations that inhibited overall RNA synthesis. (33 refs.)

- 77-6218 Semichronic Oral Toxicity of Cadmium. 2. Studies on Dogs.** (Eng) Loeser, E. (Institut für Toxikologie, Bayer A. G., Wuppertal, W. Germany); Lorke, D. *Toxicology* 7(2): 225-232; 1977.

The possible effect of small oral cadmium intake was studied in beagle dogs. Cadmium (CdCl₂) was given with the feed in concentrations of 0, 1, 3, 10, and 30 ppm during a 3-month period to groups of two male and two female dogs each. The appearance, behavior, food consumption, growth and mortality of the treated dogs in all groups were not affected. No adverse effects were detected in the blood, liver or kidney of treated animals, and their blood pressure was within the normal range. Autopsies and histopathological investigation revealed no evidence of any damage. The kidneys had the highest concentration of cadmium, followed by the liver, pancreas and salivary glands. Cadmium accumulation in these organs was dose-dependent as was cadmium excretion in the feces. (8 refs.)

77-6219 **Lead Poisoning and Brain Tumors in Children:** A Report of 2 Cases. (Eng) Schreier, H. A. Child Development Lab., Massachusetts General Hosp., Boston, MA 02114; Sherry, N.; Shaughnessy, E. *Ann Neurol* 1(6): 599-600; 1977.

Lead poisoning and subclinical body lead elevations have become increasingly prevalent in children, not only in the inner cities but in the suburbs and rural areas as well. Case reports are presented for two institutionalized children with elevated urinary lead levels (0.1 mg/liter) who subsequently developed astrocytomas. Lead toxicity may play a role in causing mental retardation, hyperactivity, and more subtle neuropsychological dysfunction in children. It has a direct toxic effect on neurons, causing astrocytic proliferation in humans and CNS neoplasms in rats. (20 refs.)

77-6220 **Inactivity of Two Noble Metals as Carcinogens.** (Eng) Furst, A. (Inst. Chemical Biology, Univ. San Francisco, San Francisco, CA 94117); Schlauder, M. C. *Environ Pathol Toxicol* 1(1): 51-57; 1977.

The potential carcinogenicity of silver and gold was evaluated by suspending fine (-300 mesh) powders of each metal in trioctanoin and injecting them in Fischer-344 rats. Cadmium powder was tested as the positive control; the vehicle alone served as the negative control. No tumors appeared at the site of injection in the silver-treated animals. The vehicle control (trioctanoin) and gold-treated groups each developed a single fibrosarcoma. In contrast, 60% of the cadmium-treated rats developed fibrosarcomas at the injection site. The mean survival time for the cadmium-injected group was 16.5 mo but for all other groups it was approx 23.5 mo. It is concluded that silver and gold are not carcinogenic when administered as finely divided powders. (18 refs.)

77-6221 **Effects of Potassium Dichromate on DNA Synthesis in Hamster Fibroblasts.** (Eng) Levis, A. G. (Inst. Animal Biology, Univ. Padua, 35100 Padua, Italy); Buttignol, M. *Br J Cancer* 35(4): 496-499; 1977.

The effect of potassium dichromate (PD) on DNA synthesis in BHK fibroblasts was investigated. When cultures were exposed to PD for 1 hr at concentrations ranging from 10^{-7} to 10^{-5} M, no significant changes in incorporation of labeled thymidine were noted. After treatment with 10^{-4} M PD, however, the specific radioactivity of DNA was at first sharply decreased; after 6 hr it increased, reaching values seven times that of controls. This result was attributed to an increase in labeled thymidine in the intracellular pool related in turn to a reduction of hexavalent chromium on the plasma membrane. Inhibition of DNA synthesis increased with duration of treatment and was greater when Hank's balanced medium

was added. Hank's medium stimulated thymidine uptake as compared to complete growth medium. (21 refs.)

77-6222 **Preliminary Experimental Study on Carcinogenicity of Arsenic Trioxide in Rat Lung.** (Eng) Ishinishi, N. (Dept. Hygiene Faculty Medicine, Kyushu Univ., Fukuoka, Japan); Kodama, Y.; Nobutomo, K.; Hisanaga, A. *Environ Health Perspect* 19: 191-196; 1977.

Male Wistar-King albino rats were divided into eight groups according to the following exposure regimen: (1) 2.5 mg of Kinkaseki copper ore (approx 0.1 mg arsenic); (2) 2.0 mg of flue dust (approx 0.2 mg arsenic); (3) 0.26 mg of arsenic trioxide (As_2O_3); (4) 0.4 mg of benzo(α)pyrene (BP) as positive control; (5) 2.5 mg ore + 0.4 mg BP; (6) 2.0 mg flue dust + 0.4 mg BP; (7) 0.2 mg As_2O_3 + 0.4 mg BP; and (8) saline as a control group. The materials were instilled intratracheally, with all rats receiving a total of 15 weekly exposures over 4 mo. Squamous cell carcinoma was not induced in the groups without BP, although lung adenocarcinoma was seen in 1/7 survivors in Group 2. All rats in Groups 1-3 did have squamous cell metaplasia in the airway or osteometaplasia in the alveolus of the lung. The incidence of lung carcinoma was 1/7 rats in Group 4, 2/10 rats in Group 5, 3/10 rats in Group 6, and 3/7 rats in Group 7. Squamous cell metaplasia in the lining cells and osteometaplasia in the alveolar cells were observed in almost all of these rats. A significant difference in malignant lung tumor incidence was noted only between Group 1-3 combined (4.0%) and Groups 4-6 combined (29.6%). It was concluded that solid arsenical substances, such as As_2O_3 , metal ore, and flue dust, tend to act as cocarcinogens with BP. (7 refs.)

77-6223 **Arsenical Air Pollution and Lung Cancer (Letter to Editor).** (Eng) Lyon, J. L. (Div. Epidemiology, Dept. Family and Community Medicine, Univ. Utah, Salt Lake City, UT 84132); Fillmore, J. L.; Klauber, M. R. *Lancet* 2(8043): 869; 1977.

A study was made to determine whether there is an association between distance from a smelter releasing arsenic into the air and lung cancer. Lymphoma cases in the same area were used as controls. Contrary to a previous study, it was found that closeness to the smelter did not increase the risk of lung cancer. However, there was no control for smoking in either study. (6 refs.)

77-6224 **Comparative Measurements of the Short-term Lung Clearance and Translocation of PuO_2 and**

Mixed $\text{Na}_2\text{O} + \text{PuO}_2$ Aerosols in Mice (Meeting Abstract). (Eng) Brightwell, J. (No affiliation given); Carter, R. F. *Ann Occup Hyg* 20(2): 204; 1977. (no refs.)

77-6225 **Studies on Mutagenicity of Mineral Oils (Meeting Abstract).** (Eng) Hermann, M. (Lab. Genetic Toxicology, Pasteur Inst., Paris, France); Weill-Thevenet, N.; Bedouelle, H.; Hofnung, M. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 64; 1977. (no refs.)

77-6226 **Thyroid Hormone Measurements in Experimental Thyroid Cancer in Rats.** (Eng) Al-Hindawi, A. Y. (Inst. Radiology and Nuclear Medicine, Baghdad, Iraq); Black, E. G.; Brewer, D. B.; Griffiths, S. G.; Hoffenberg, R. In: *Radiation-associated Thyroid Carcinoma*. DeGroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): 539 pp.; 215-216; 1977.

Rats were inoculated ip with 25 μCi of ^{131}I followed by propylthiouracil (PTU, 60 $\mu\text{g}/\text{ml}$ drinking water), thyroxine (T_4 , 0.5 $\mu\text{g}/\text{ml}$ drinking water), or PTU + T_4 . Thyroid tumors were induced by ^{131}I , PTU, and T_4 but only after prolonged elevation (7-9 mo) of serum thyrotropin levels. The tumor-bearing rats had normal levels of serum T_4 , T_3 , free T_4 , and free T_3 . (no refs.)

77-6227 **Biotransformation of Diethylstilbestrol in the Rhesus Monkey and the Chimpanzee.** (Eng) Metzler, M. (Institut für Pharmakologie und Toxikologie, Universität Würzburg, Versbacher Landstrasse 9, 8700 Würzburg, W. Germany); Müller, W.; Hobson, W. C. *J Toxicol Environ Health* 3(3): 439-450; 1977.

The metabolism of diethylstilbestrol (DES) was studied in rhesus monkeys and chimpanzees. Four days after a po dose of 1 mg/kg ^{14}C -DES, approx 59% of the ingested radioactivity was found in the urine and 28% in the feces of two female rhesus monkeys. In male rhesus monkeys, urinary radioactivity accounted for 43% and fecal radioactivity for 35%. In chimpanzees, 63% of a 0.5 mg/kg dose was excreted with the urine in a female and 47% in a male. In both species, urinary radioactivity was predominantly (> 70%) associated with glucuronides. Besides DES, three metabolites were found in the urinary glucuronide fraction of rhesus monkeys and chimpanzees by radio gas chromatography, and they were identified as dienestrol and the ω -hydroxy derivatives of DES and dienestrol. Fecal radioactivity in rhesus monkeys consisted exclusively of DES. Glucuronidation of DES appears to occur in neonatal and fetal rhesus monkeys. (20 refs.)

77-6228 **Stilboestrol (Diethylstilbestrol) and the Risk of Ovarian Cancer.** (Eng) Hoover, R. (Environmental Epidemiology Branch, NCI, Bethesda, MD 20014); Gray, L. A.; Fraumeni, J. F. *Lancet* 2(8037): 533-534; 1977.

A follow-up study was conducted of 908 women who were treated po with premarin (conjugated equine estrogen) for at least 6 mo. Eight ovarian cancers and one cancer of the fallopian tube were observed, a rate that was two to three times greater than that expected. The risk increased with the strength of the premarin tablet taken, but not with duration of use or total accumulated dose. No significant trends were noted with respect to age at first premarin use or interval between first use and the diagnosis of cancer. However, this excess risk of ovarian cancer was limited to 99 women who had also taken other estrogens, mainly conjugated estrogens identical or similar to premarin. Ovarian cancers occurred in four patients in this group, and three of these patients had taken stilbestrol for \geq yr. The expected value in the 21 patients in this series who had taken stilbestrol in addition to premarin was 0.1. The three tumors occurred in 12-19 yr after use of the drug. (12 refs.)

77-6229 **Pathological Changes in Female C3H Mice Continuously Fed Diets Containing Diethylstilbestrol or 17 β -Estradiol.** (Eng) Highman, B. (Natl. Center for Toxicological Res., Jefferson, AR 72079); Norvell, M. J.; Shellenberger, T. E. *J Environ Pathol Toxicol* 1(1): 1-30; 1977.

Pathology studies were conducted with C3H/HeJ mice fed diethylstilbestrol (DES: 10, 100, or 500 ppb) or 17 β -estradiol (E_2 : 100, 1,000, or 5,000 ppb) from age 6 to 110 wk and with C3HeB/FeJ mice fed DES (10, 100, or 500 ppb) from age 6 to 136 wk. A total of 396 mice were sacrificed at 52 wk and > 500 others at intervals up to 102 wk. After 52 wk on 500 ppb DES or 5,000 ppb E_2 , the cervix often showed stromal mucoid changes and adenosis characterized by focal replacement of squamous epithelium by columnar epithelium lining the cervical canal. The uterine horns showed hyperplastic glands, which often penetrated the muscularis, and focal endometrial and perivascular hyalin deposits. The ovaries showed atrophy, with absence of the corpora lutea. Ceroid deposits were increased in the ovaries and adrenals. The incidence of uterine cervical adenosis and of mammary hyperplastic alveolar nodules and tumors (mainly type B, Dunn's classification) was higher in C3H/HeJ than in C3HeB/FeJ mice. Changes in the mice on lower doses of DES or E_2 were less frequent but similar. The tumors in estrogen-treated mice included 4 endometrial adenocarcinomas and an adenoacanthoma of a uterine horn, 14 cervical adenocarcinomas, 1 vaginal squamous cell carcinoma, 1 cervical granular cell myoblastoma, 1 sternal and 3 cranial osteosarcomas, and 1 mesothelioma. Most of the malignancies occurred in C3H/HeJ mice. The mammary tumor virus factor facilitates DES-

induced mammary tumorigenesis in C3H mice, and it may contribute to other DES-induced malignant and premalignant lesions. (19 refs.)

- 77-6230 **Blockage of the Occurrence of Permanent Vaginal Changes in Neonatally Estrogen-treated Mice by Vitamin A; Parabiosis and Transplantation Studies.** (Eng) Yasui, T. (Dept. Biology, Faculty Science, Okayama Univ., Tsushima, Okayama-shi 700, Japan); Iguchi, T.; Takasugi, N. *Endocrinol Jpn* 24(4): 393-398; 1977.

In ovariectomized C57-Black/Tw mice that had received neonatal sc injections of 20 μ g estradiol-17 β (E₂), the occurrence of permanent proliferation and cornification of the vaginal epithelium was prevented by injections of 200 IU vitamin A acetate (VA) given simultaneously with E₂. When neonatally E₂-treated mice were parabiotically joined with ovariectomized mice treated neonatally with E₂ plus VA, the permanent vaginal changes were suppressed in the E₂ parabionts after 97-110 days of union. These permanent changes were also suppressed by transplantation of vaginas from the E₂-treated donors into the E₂ plus VA-treated hosts. A possible mechanism for the degeneration of permanently changed vaginal epithelium is discussed. (10 refs.)

- 77-6231 **Exogenous Oestrogens and Ovarian Cancer (Letter to Editor).** (Eng) Annegers, J. F. (Dept. Medical Statistics and Epidemiology, Mayo Clinic, Rochester, MN 55901); O'Fallon, W.; Kurland, L. T. *Lancet* 2(8043): 869-870; 1977.

A study made in Rochester, MN, contradicts a previously reported association between the use of exogenous estrogens (for \geq 6 mo) and ovarian cancer. The present study was done in the same manner as the previous one. Upon reevaluation of the previous data the association was found to be not as strong as suggested. (4 refs.)

- 77-6232 **Mammary Carcinogenesis in Castrated (C3H x RIII)F₁ Male Mice Bearing Ovarian Transplants in the Ear for Variable Periods of Time.** (Eng) Muranyi-Kovacs, I. (Unite 119 de l'INSERM, 27, boulevard Lei Roure, 13009 Marseille, France); Rudali, G.; Assa, R. *Eur J Cancer* 13(11): 1351-1356; 1977.

With the passage of time, the presence of an ovarian transplant on the ears of castrated male (C3H x RIII)F₁ mice decreased latency time and increased the frequencies of mammary tumors. A month was required for the ovarian transplant to stimulate mammary carcinogenesis. The presence of an ovarian graft for 2 mo or throughout the life of the animal

induced mammary tumors at a similar frequency. However, 3-mo graft was necessary to obtain latency times of tumors similar to those observed in animals bearing lifelong grafts. Castrated males bearing ovarian grafts for 2-3 mo may be a useful model for studying the role of ovarian secretions in mammary carcinogenesis. (13 refs.)

- 77-6233 **Prolactin, Oestrogen, and Lipids in Breast Fluid.** (Eng) Wynder, E. L. (American Health Foundation, 1370 Ave. Americas, New York, NY 10019); Hill, P. *Lancet* 2(8043): 840-842; 1977.

Prolactin, estrogen, and lipid concentrations were measured in the plasma and breast-duct fluid of eight nonlactating, premenopausal women with no history of breast disease. The concentrations of prolactin, estrogen, and triglycerides were significantly higher in the ductal fluid than in the plasma, but there was little difference in cholesterol levels. The high prolactin and estrogen concentrations found in the ductal fluid of Western women may be related to their incidence of invasive intraductal breast cancer. (19 refs.)

- 77-6234 **Dietary Fat, Hormones and Breast Cancer (Meeting Abstract).** (Eng) Chan, P. C. (Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY 10595). In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 22; 1977. (no refs.)

- 77-6235 **Mammary Gland Carcinogenesis by Progesterone in the Mouse; Dosage Effect (Meeting Abstract).** (Eng) Ropcke, G. (Netherlands Cancer Inst., Amsterdam, The Netherlands); Boot, L. M. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 22; 1977. (no refs.)

- 77-6236 **Progesterone Promotes Diethylnitrosamine Induced Tumour Growth in Rats (Meeting Abstract).** (Eng) Desser-Wiest, L. (Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A-1090 Vienna, Austria). In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 26; 1977. (no refs.)

- 77-6237 **Primary Liver Tumors and Oral Contraceptives: Results of a Survey.** (Eng) Vana, J. (Dept.

Epidemiology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263); Murphy, G. P.; Aronoff, B. L.; Baker, H. W. *JAMA* 238(20): 2154-2158; 1977.

Data on 378 female and 165 male cases of primary liver tumors reported by 477 hospitals in the US from 1970 to 1975 show that 91.5% of the tumors were malignant in men, and 43.9% were malignant in women. Of the 212 benign tumors in women, 96 were hepatic cell adenomas and 58 were focal nodular hyperplasias. A history of oral contraceptive use was found in 65% of the women with benign tumors, 74% with hepatic cell adenomas, and 74% with focal nodular hyperplasias. The symptoms were more severe among users. No case of ip bleeding was observed in nonusers. The findings confirm the suggested association between oral contraceptive use and hepatic cell adenomas and focal nodular hyperplasias. (20 refs.)

77-6238 Primary Carcinoma of the Liver and Long-term Administration of Oral Contraceptives Followed by Pregnancy. (Ger) Balazs, M. (Pathologische Abteilung, Janos-Krankenhaus, Diosarok u. 1, 1125 Budapest, Hungary); Gergely, R.; Winkler, G. *Dtsch Med Wochenschr* 102(41): 1472-1474; 1977.

A case is reported of a 32-yr-old woman who took oral contraceptives for 7 yr, gave birth to a normal child after discontinuing the drugs, and died 3 mo later from a poorly differentiated hepatocellular hepatoma. The tumor cells contained fibrils similar to alcoholic hyalin. The role of the oral contraceptives and the hormonal influence of pregnancy in the development of the malignant tumor are discussed. (51 refs.)

77-6239 Toxicity of DU 41274, an Experimental Gestagen, in the Beagle Dog after Oral Administration for 50 Weeks. (Eng) Rivett, K. F. (Huntingdon Res. Centre, Huntingdon, England); Heywood, R.; Saxena, S. C.; Offringa, O. R. *Proc Eur Soc Toxicol* 18: 291-293; 1977.

The toxicity of DU 41274 (17-ethoxy-6-fluoro-1 α ,2 α -dihydro-3'H-cyclopropa [1,2]-9 β ,10 α -pregna-1,4,6-triene-3,20-dione) was investigated in groups of three male and three female 16- to 19-wk-old beagles who received po doses of 0.08, 0.24, or 0.80 mg/kg/day for 50 wk. Animals receiving 0.24 and 0.80 mg/kg/day gained more wt than controls without increased food consumption. Clinical changes noted were an absence of estral changes and mammary gland development in all females from week 8 and in two males from weeks 9 to 13 (at 0.80 mg/kg/day). Total serum proteins were higher in the animals on the two highest regimens than in controls. A mammary nodule was detected during week 25 in one female on the highest dose; it proved to be a well-circumscribed adenoma. Between 31 and 49 wk, deeply situated mammary nodules were noted in all treated females and

in two control females. Hyperplasia of the mammary gland acini and ducts with secretory activity, arrested ovarian maturation, and the absence of corpora lutea were found at autopsy of all treated females. Endometrial and hypophyseal changes, including atrophy, were also evident. Gallbladder hyperplasia was present in one female receiving 0.24 mg/kg/day. All nodules excised at autopsy were lymph nodes, except for the one adenoma. (6 refs.)

77-6240 In Vitro Binding of β -Propiolactone to Calf Thymus DNA and Mouse Liver DNA to Form 1-(2-Carboxyethyl)adenine. (Eng) Mate, U. (Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Sch. Medicine, New York, NY 10016); Solomon, J. J.; Segal, A. *Chem Biol Interact* 18(3): 327-336; 1977.

The in vitro binding of 100 μ l of β -propiolactone to calf thymus DNA and female ICR/Ha mouse liver was investigated. Acid hydrolysis of the reacted DNA resulted in the isolation of 1-(2-carboxyethyl)adenine (1-CEA). Assignment of the structure of this compound was based on UV spectra at acidic, alkaline, and neutral pH and electron impact and chemical ionization mass spectra. It was confirmed by chemical synthesis of 1-CEA from β -propiolactone and 2'-adenosine-5'-monophosphoric acid. The formation of 1-CEA interrupts the Watson-Crick base-pairing between adenine and thymine by blocking hydrogen bonding of the bases. It is not known if the presence of 1-CEA in DNA results in DNA activation, mutation, or repair. (36 refs.)

77-6241 Lack of Carcinogenicity of Oxprenolol, A β -Adrenergic Blocking Agent. (Eng) Newberne, J. W. (Merrell-Natl. Labs., Richardson-Merrell, Incorporated, Cincinnati, OH 45215); Newberne, P. M.; Gibson, J. P.; Huffman, K. W.; Palopoli, F. P. *Toxicol Appl Pharmacol* 41(3): 535-546; 1977.

The carcinogenicity of oxprenolol (Oxp), a β -adrenergic blocking agent, was determined in Carworth CF/1 mice administered 0, 15, 50, and 150 mg/kg/day of the compound in a commercial diet for 6 or 18 mo. All animals were sacrificed by 21 mo. Although the compound inhibited wt gain, especially in females, no carcinogenic effects could be discerned. In another experiment, using a semisynthetic diet, the mice were given 150 mg/kg/day of Oxp or pronethalol in the diet for 18 mo. As a positive carcinogen control, additional mice were exposed to 0.03% 2-acetylaminofluorene (2-AAF) for 12 mo. Mice fed 2-AAF had a high incidence of liver carcinoma, but those fed pronethalol or Oxp had no increased incidence of tumors over controls. In a third experiment, Charles River rats of the Sprague-Dawley strain were fed Oxp for 18 mo in a commercial diet at doses of 0, 15, 50, and 150 mg/kg/day; all animals were sacrificed by 18 mo. In spite

of a modest drug-related inhibition of wt gain, no significant increase in tumors was noted. It is concluded that Oxp is not carcinogenic in the species tested; the results with pronethalol are at variance with previous findings. (5 refs.)

- 77-6242 **Preliminary Report on the Carcinogenic Dose-response Curve to Oral Vitamin D₂.** (Eng) Gass, G. H. (Endocrinologic Pharmacology Res. Lab., Southern Illinois Univ., Carbondale, IL 62901); Allaben, W. T. *IRCS Med Sci: Cancer* 5(10): 477; 1977.

Mammary tumor virus positive C3H mice fed 0.5 or 1.0 ppm vitamin D₂ for 24 mo showed a decrease in tumor latent period relative to controls. Animals receiving the above two doses, or 2.0 or 4.0 ppm had a greater tumor incidence at 18 mo than controls. Administration of 60 to 960 IU of vitamin D₂ resulted in a significant increase in mammary carcinoma, a decrease in latent period and signs of toxicity at high dose levels. (6 refs.)

- 77-6243 **Changes in Laryngeal Mucosa Produced Experimentally by Endogenous and Exogenous Factors in Mice.** (Ger.) Kambic, V. (Otorhinolaryngologische Klinik der Medizinischen Fakultät, Yu-61000, Ljubljana, Yugoslavia); Radsel, Z.; Zargi, M. *HNO* 25(7): 249-252; 1977.

The effects of exogenous factors on the hormonally altered laryngeal mucosa of Albany mice were studied. Two groups of eight males received either no treatment or testosterone (150 µg/day, ip); two groups of eight ovariectomized females received either no treatment or testosterone (same dose as above). The mice were exposed to cigarette smoke for 1 hr/day x 6 wk. Histopathological examination showed that the larynx can be considered a target organ for male hormones and that exogenous factors (such as cigarette smoke) produce changes that lead to malignancy. (10 refs.)

- 77-6244 **Multiple Hepatic Adenomas and a Hepatocellular Carcinoma in a Man on Oral Methyl Testosterone for Eleven Years.** (Eng) Boyd, P. R. (James Homer Wright Pathology Lab., Massachusetts General Hosp., Boston, MA 02114); Mark, G. J. *Cancer* 40(4): 1765-1170; 1977.

A 29-yr-old man developed numerous small hepatic adenomas and hepatocellular carcinoma after 11 yr of po methyltestosterone treatment, which was initiated 2 yr after removal of a craniopharyngioma. This appears to be the first reported case of both benign and malignant liver neoplasms associated with anabolic steroid therapy. (43 refs.)

- 77-6245 **Irreversible Lesions in Female Reproductive Tracts of Mice after Prenatal Exposure to Testosterone Propionate.** (Eng) Taguchi, O. (Lab. Experimental Pathology, Aichi Cancer Center Res. Inst., Chikusa-ku, Nagoya 464, Japan); Nishizuka, Y.; Takasugi, N. *Endocrinol Jpn* 24(4): 385-391; 1977.

The effect of a single sc injection of testosterone propionate (TP) on female C3H/HeMs mice was investigated. All fetuses were given a dose of 250, 25, 1.25 or 0.125 µg of TP on day 15 or 17 of prenatal life, and female newborns were injected with the same doses on the first day of life. All females were ovariectomized at 3 to 8 mo, adrenalectomized 30 days later, and killed 14 to 30 days after the second operation. None of the control mice had vaginal or uterine lesions, failure of the vaginal opening to form, absence of the corpora lutea, or sterility. Of nine mice receiving a 250 µg injection on day 17, nine had vaginal and two had uterine lesions, nine had failure of the vaginal opening to form and consequent sterility, and one lacked corpora lutea. Of 18 animals receiving similar treatment at birth, 17 had vaginal and 5 had uterine lesions, 13 lacked corpora lutea in the ovaries, and all were sterile. Of nine mice receiving 25 µg dose at day 17, nine had vaginal and six had uterine lesions, two lacked vaginal opening, and eight were sterile. Of the five treated at day 15, all had vaginal lesions, lacked vaginal openings, and were sterile. Of 12 animals treated at birth, 9 had vaginal lesions, 3 lacked corpora lutea in the ovary, and 10 were sterile. Of nine animals treated with 1.25 µg at day 17, all had vaginal and one had uterine lesions, two lacked vaginal openings, and three were sterile. Of six animals treated at day 15, five had vaginal lesions. Of 16 treated at birth, 11 had vaginal lesions and 3 were sterile. In the lowest dosage group, of 12 animals treated at day 17, 4 had vaginal lesions; of 11 treated at day 15, 1 had a vaginal lesion; and no pathology was observed in 20 treated at birth. The vaginal cornifications and uterine stratifications were irreversible and ovary-independent. (12 refs.)

- 77-6246 **Multiple Tumors after Androgen Therapy.** (Eng) Sale, G. E. (Div. Oncology, Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA 98104); Lerner, K. G. *Arch Pathol Lab Med* 101(11): 600-603; 1977.

A 37-yr-old man developed multiple small well-differentiated hepatomas with early peliosis hepatis, multiple pancreatic islet cell tumors, and a renal medullary interstitial cell tumor after 5 yr of androgen and prednisone therapy for idiopathic aplastic anemia. He died shortly after allogeneic bone marrow transplantation. The hepatic tumors were well-differentiated, and the pancreatic tumors were of a mixed ribbon and islet cell pattern. The therapeutic and experimental implications and the relevant literature are summarized briefly. (26 refs.)

- 77-6247 **Prostatic Carcinoma: Castration Alters the Metabolism of Catecholamine and 5-Hydroxytryptamine.** (Eng) Agarwal, R. A. (Dept. Pharmacology, Faculty Medicine, Univ. Ottawa, Ottawa, Canada K1N 9A9); Rastogi, R. B.; Singhal, R. L. *Gen Pharm* 8(3): 197-200; 1977.

The metabolism of norepinephrine (NE), dopamine (DA), and 5-hydroxytryptamine (5-HT) was examined in methylcholanthrene-induced rat prostate carcinoma, and the question of whether androgenic deprivation affects the biosynthesis capacity of these putative transmitters was investigated. A suspension of cells from an induced squamous epithelial cell carcinoma was implanted under the skin of castrated (24 hr earlier) or intact male Fisher rats. Rats were sacrificed 14 days after implantation, and tumor tissue was removed for analysis. The ventral prostate of normal rats was used as a control. Tyrosine hydroxylase (TH), tyrosine (TR), monoamine oxidase (MAO), catechol-O-methyltransferase (COMT), DA, 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), and tryptophan (TP) were found in the prostatic carcinoma. The levels of DA, MAO, and COMT were significantly higher than those of normal prostatic tissue; the levels of the remaining substances were significantly lower. NE was present in the normal ventral prostate but was not detectable in the epithelial cells of the malignant prostate in either intact or castrated rats. In the tumors grown in castrated rats, DA, TH, TR, 5-HT, TP, and 5-HIAA levels were significantly lower than those found in the tumors of intact animals. These findings show that castration reduces the levels of biogenic amines and the activity of the synthesizing enzyme TH in tumor tissue. The results indicate that prostatic carcinoma cells may actually be synthesizing DA and 5-HT, a process that is androgen-dependent and may have an important role in the maintenance of carcinoma. (20 refs.)

- 77-6248 **VinylethylNitrosamine: A Potent Respiratory Carcinogen in Syrian Hamsters.** (Eng) Althoff, J. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NB 68105); Grandjean, C.; Russell, L.; Pour, P. *J Natl Cancer Inst* 58(2): 439-442; 1977.

VinylethylNitrosamine (VEN) was synthesized, and its chronic effect was examined in 30 male and 30 female Syrian hamsters after they were inoculated sc with 0.1 of the LD₅₀ (10 mg/kg) once weekly for life. Distribution studies showed that the max amount of unaltered compound was found in various tissues 45 min after injection. VEN was only partially excreted unchanged after 5 hr. The highest levels were in the circulating blood, followed by the liver and pancreas. The hamsters had a 100% tumor incidence by the end of 28 wk, when all had died. There was an av of 1.9 tumors per animal in different organ systems, and multiple neoplasms were observed in different organ segments. Tumors of the respiratory

tract with short latencies and tumors of the upper digestive tract and pancreas predominated. All animals showed extensive hyperplasia, squamous cell metaplasia, and dysplasia, often throughout the respiratory epithelium. All respiratory carcinomas were locally invasive with no distant metastases. The major tumor types were papillary polyps, epidermoid carcinomas, and adenocarcinomas. It was concluded that VEN is a more potent carcinogen than diethylenitrosamine. (18 refs.)

- 77-6249 **The Effect of Temperature During the Diethylnitrosamine Treatment on Liver Tumorigenesis in the Fish, *Oryzias latipes*.** (Eng) Kyono, Y. (Zoological Inst., Faculty Science, Univ. Tokyo, Tokyo 113, Japan); Egami, N. *Eur J Cancer* 13(10): 1191-1194; 1977.

Fish (*Oryzias latipes*) kept at room temperature (25 C) during treatment with 100 ppm diethylnitrosamine (DENA) for 8 wk developed hyperbasophilic liver nodules, some of which appeared to be trabecular hepatomas and liver cell carcinomas. Tumor nodules were also observed in 50% of the fish treated with 50 ppm DENA at 25 C. In contrast, the majority of fish kept at 8 C had no nodules even when 100 ppm DENA was administered. Although one fish treated with the high DENA dose at the low temperature developed a hyperbasophilic cell mass, this growth was markedly smaller than the nodules in the room-temperature group. It is suggested that the histological changes observed at 8 C were related to the toxic effects of DENA, as distinct from its tumorigenic effects. (9 refs.)

- 77-6250 **Multi-hit Kinetics of Tumor Formation, with Special Reference to Experimental Liver and Human Lung Carcinogenesis and Some General Conclusions.** (Eng.) Emmelot, P. (Div. Chemical Carcinogenesis, Antoni van Leeuwenhoek-Huis, Netherlands Cancer Inst., Amsterdam, Netherlands); Scherer, E. *Cancer Res* 37(6): 1702-1708; 1977.

A formula based on dose-response kinetics has been derived for calculating the number of required hits for tumor formation. Analysis of experimental data for the induction of highly malignant liver tumors in rats by continuously administered diethylnitrosamine (DEN), a strong carcinogen exhibiting low toxicity, concluded that seven hits are required for lethal tumor formation. Calculations for a single dose of DEN (50-100 mg) indicated that induction of trabecular carcinoma is initiated by no more than two concomitant hits, followed by three spontaneous events. Tumors appear to be induced as a result of specific events caused by: (1) the carcinogen applied and (2) background events, such as spontaneous changes and/or hits by carcinogenic stimuli from the environment or by those present endogenously. The relative con-

tribution of these two events may shift according to the dose and potency of the carcinogen. At low doses of a weak carcinogen, as in the case of cigarette smoke, induction appears to be a one-hit process in conjunction with one or more background hits. (45 refs.)

- 7-6251 **Quantitative Analyses of Enzyme-deficient Cell Areas to Assess Early Precancerous Alterations of Hepatocarcinogenic Substances (Meeting Abstract).** (Eng) Kunz, W. (DKFZ, Heidelberg, W. Germany); Appel, K. E.; Rickart, R.; Stoeckle, G. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 45; 1977. (no refs.)

- 7-6252 **Histopathology of Preneoplastic and Neoplastic Lesions of the Esophagus in BUF Rats Ingesting Diethylnitrosamine.** (Eng) Reuber, M. D. (11014 Swansfield Rd., Columbia, MD 21044). *J Natl Cancer Inst* 58(2): 313-321; 1977.

The histopathology of preneoplastic and neoplastic lesions was studied in the esophagus of BUF male and female rats given diethylnitrosamine (DEN; 0.014%) in the diet for 26 wk. Surviving animals were given basal diet for an additional 10 wk. The carcinomas were focal and located in three portions of the esophagus: (1) the upper part adjacent to the pharynx; (2) the bifurcation of the trachea; (3) at the level of the diaphragm. Young males developed more carcinomas than young females, and old rats were resistant to esophageal carcinoma. The stages of hyperplasia, hyperplastic nodules, small carcinomas, and large, well-developed carcinomas were observed. The carcinomas, which were well-differentiated, poorly differentiated, or undifferentiated, invaded the adjacent tissue but did not metastasize. The rats generally died from bronchopneumonia before metastases had time to develop. (14 refs.)

- 7-6253 **Cytoplasmic Changes in Level and Distribution of Glucose-6-phosphatase Activities from Rat Liver During Diethylnitrosamine-induced Carcinogenesis.** (Eng) Eltze, M. (Byk Gulden, D-755 Konstanz, W. Germany); Jung, A.; Jackisch, R. *Chem Biol Interact* 18(3): 295-308; 1977.

The level and distribution of glucose-6-phosphatase (G-6-P) activity in isolated hepatic cytoplasmic compartments of female Wistar rats fed diethylnitrosamine at a dose of 2.6 mg/kg/day in the drinking water for 20 wk were examined. The wt of the rats fed the carcinogen remained lower than

that of controls, but the wt of the livers undergoing neoplastic change increased in size and wet wt. About 70% of the G-6-P activity was detected in the microsomal fraction. After the fourth week of carcinogenesis, there was a distinct decrease in enzyme activity in this fraction compared with normal rats. A comparison of the microsomal subfractions revealed that the smooth membrane fractions I and II had a significant deviation in enzyme activity from controls after 8 wk. No significant differences were detected in the rough membrane fractions I and II or in the ribosomal/polyribosomal pellets. The earliest differences in enzyme activity were detected in smooth membrane fraction II after 4 wk of induction. Thus, part of the activity appears to be detached from the heavier cytoplasmic components and transferred to the smooth membrane fraction II early in carcinogenesis. (34 refs.)

- 77-6254 **Inhibition of Dimethylnitrosamine-induced Strand Breaks in Liver DNA and Liver Cell Necrosis by Diethyldithiocarbamate.** (Eng) Abanobi, S. E. (Fels Res. Inst., Temple Univ., Sch. Medicine, Philadelphia, PA 19140); Popp, J. A.; Chang, S. K.; Harrington, G. W.; Lotlikar, P. D.; Hadjiolov, D.; Levitt, M.; Rajalakshmi, S.; Sarma, D. S. *J Natl Cancer Inst* 58(2): 263-271; 1977.

The mechanism by which diethyldithiocarbamate (DEDTC) prevents dimethylnitrosamine (DMN)-induced strand breaks in liver DNA and liver cell necrosis in male Wistar rats was investigated. Strand breaks were detected in the liver DNA from a rat that received 0.14 micromole (μmol) DMN/g 4 hr before being killed. No strand breaks were detected, however, in rats given 0.07 or 0.14 μmol DMN/g after pretreatment with 2.9 μmol DEDTC. DEDTC did not inhibit fragmentation of liver DNA caused by other carcinogens, such as N-hydroxy-2-acetylaminofluorene, 3-hydroxyxanthine, aflatoxin B₁, N-acetoxy-2-acetylaminofluorene, methyl methanesulfonate, methylnitrosourea, and methylazoxymethanol acetate, whether or not they required metabolic activation. The inhibitory effect of DEDTC was transitory, and protection for 4 hr required multiple injections of DEDTC (2.9 μmol DEDTC/g, 3 times, 4 hr apart). DEDTC also inhibited the serum clearance of DMN, methylation of liver DNA, and oxidative demethylation of DMN in the in vitro hepatic microsomal system prepared from male Wistar rats or from hamsters, as well as DMN-induced hepatocytic ultrastructural changes and necrosis. It is concluded that DEDTC prevents the DMN-induced strand breaks in liver DNA and other biochemical and morphologic changes by inhibiting its metabolism. (58 refs.)

- 77-6255 **Decreased Incidence of Renal Tumors in DMN Treated Balb/c Mice after Orchiectomy.** (Eng) Noronha, R. F. (Dept. Surgery, Section Urology, St. Louis Univ. Sch. Medicine, 1325 S. Grand Blvd., St. Louis, MO 63104). *J Surg Oncol* 9(5): 463-468; 1977.

The influence of male hormones on the progression of renal tumors was investigated in male inbred BALB/c mice. Two groups of mice were inoculated ip with 10 mg/kg dimethylnitrosamine (DMN) at 60 or 80 days of age, and the latter group underwent orchiectomy 120 days later. A third group of mice underwent orchiectomy only at 200 days of age, and a fourth group was untreated (controls). In 35 untreated controls, the incidence of lung tumors, kidney tumors, lymphomas, hepatomas, and liver hemangiomas was 20%, 0%, 8.6%, 5.7%, and 2.9%, respectively. In 34 animals treated with orchiectomy only, the respective incidences were 50%, 0%, 20.6%, 2.9%, and 2.9%. In 44 DMN-treated animals, incidences were 81.8%, 45.5%, 9.1%, 15.9%, and 18.1%, and in 43 animals treated with DMN + orchiectomy, the incidences were 83.7%, 25.6%, 9.3%, 16.2%, and 16.2%. Orchiectomy decreased the incidence of renal tumors, which indicates that androgens are involved in the development and progression of nitrosamine-induced renal tumors in adult mice. These results could explain the failure of androgenic substances in the treatment of metastatic renal cell cancer. (12 refs.)

- 77-6256 **DNA Synthesis Inhibition by Dimethylnitrosamine in Regenerating Rat Liver.** (Eng) Gol-Winkler, R. (Laboratoire de Biochimie Applique, Universite de Liege, 32, blvd. de la Constitution, 4020 Liege, Belgium); Goutier, R. *Eur J Cancer* 13(10): 1081-1087; 1977.

DNA synthesis was measured in the regenerating livers of female Wistar rats inoculated with dimethylnitrosamine (DMNA) at different times after partial hepatectomy and sacrificed 20-264 hr after surgery (1 hr after ³H-thymidine injection). DMNA (9 mg/kg) given 30 min after partial hepatectomy markedly inhibited the first two waves of DNA synthesis, significant ³H-thymidine incorporation being observed only 56 hr after surgery. When administered 24 hr after partial hepatectomy (at the peak of DNA synthesis in control animals), the same DMNA dose inhibited ³H-thymidine incorporation, which did not resume until 96 hr after surgery. Doses of 2, 4, 9, and 18 mg/kg DMNA were given 30 min or 24 hr after partial hepatectomy, and DNA specific activity was measured at 28 hr after surgery (1 hr after ³H-thymidine injection). DNA synthesis inhibition was usually proportional to the dose, but it was similar when the drug was injected 30 min or 24 hr after surgery. From this observation, it is concluded that DNA synthesis inhibition by DMNA administered after partial hepatectomy originates more from template alteration than from delay in enzyme synthesis. (28 refs.)

- 77-6257 **Differences in Patterns of Structural Change by Rat Liver DNA Following Administration of Dimethylnitrosamine and Methyl Methanesulfonate.** (Eng) Huang, P. H. (Sch. Pathology, Univ. New South Wales, Post

Office Box 1, Kensington, New South Wales, Australia 2033); Stewart, B. W. *Cancer Res* 37(10): 3796-3801; 1977.

The in vivo modification of Wistar rat liver DNA by the hepatocarcinogen dimethylnitrosamine (DMN) and the non-hepatocarcinogen methyl methanesulfonate (MMS) was studied by chromatography on benzoylated 2-(diethylamino)-ethylcellulose. A major DNA fraction, considered to be double-stranded, was recovered during elution with a linear NaCl gradient; a minor fraction, considered to contain single-stranded regions, was eluted with caffeine solution. The same DNA fraction was obtained by stepwise elution. Administration of DMN caused a progressive increase in the caffeine-eluted DNA fraction isolated up to 4 hr after treatment. This increase paralleled the incorporation of radioactivity following administration of an equal dose of 10 mg ¹⁴C-DMN/kg. The increase in the caffeine-eluted DNA fraction was linearly related to dose up to 30 mg/kg DMN. Injection of MMS resulted in an increase in the caffeine-eluted fraction of DNA. The increase was almost independent of dose when animals were killed 4 hr after treatment, but it was more dose-responsive in the range 30-120 mg/kg when DNA was isolated 90 min after MMS injection. A successive decrease in the size of the caffeine-eluted DNA fraction with increasing time after administration of MMS or DMN, culminating in a return to elution profiles identical with those from untreated animals, was considered evidence of DNA repair. Repair of MMS-induced damage was almost complete within 24 hr, but repair following a non-necrotizing dose of DMN required approx 4 days. The data, correlated with studies of the elimination rate of methylated bases from DNA, suggest that differences in repair patterns elicited by DMN and MMS may be directly related to the respective alkylated moieties that they produce in the DNA. (26 refs.)

- 77-6258 **Influences of Drugs Modifying Cyt. P 450 Function on Oxidative Demethylation and Alkylating Intensity of Dimethylnitrosamine (Meeting Abstract).** (Eng) Appel, K. E. (DKFZ, Heidelberg, W. Germany); Schwarz, M.; Kunz, W. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 46; 1977. (no refs.)

- 77-6259 **Effect of an Essential Fatty Acid Deficient Diet on Dimethylnitrosamine Demethylation by Rat Hepatic Microsomal Cytochrome P-450 Enzyme System.** (Eng) Canuto, R. A. (Istituto di Patologia Generale dell'Universita di Torino, Torino 10125, Italy); Poli, G.; Garcea, R.; Longhin, P. P. *IRCS Med Sci: Cancer* 5(9): 409; 1977.

The effect of a diet deficient in essential fatty acids on dimethylnitrosamine (DMN) demethylation by the male Wistar

t hepatic microsomal cytochrome P-450 system was evaluated. After an 8- to 10-wk feeding period, there was a 27% inhibition of DMN demethylase activity. Thus, the hepatotoxicity of DMN may be lower in essential fatty acid-deficient rats than in normal rats. (8 refs.)

7-6260 **13-cis-Retinoic Acid: Inhibition of Bladder Carcinogenesis Induced in Rats by N-Butyl-N-(4-hydroxybutyl)nitrosamine.** (Eng) Grubbs, C. J. (IIT Res. Inst., Chicago, IL 60616); Moon, R. C.; Squire, R. A.; Farow, G. M.; Stinson, S. F.; Goodman, D. G.; Brown, C. C.; Korn, M. B. *Science* 198(4318): 743-744; 1977.

Transitional cell carcinoma of the bladder was induced in 10/22 male Fischer rats by 12 po 200-mg doses of N-butyl-N-(4-hydroxybutyl)nitrosamine. Feeding of 13-cis-retinoic acid (240 mg/kg diet) after completion of carcinogen treatment significantly reduced the number and severity of the cancers (7/21 animals) and other proliferative lesions of the bladder. (8 refs.)

7-6261 **Stages of Transformation in the Development of N-Butyl-N-(4-Hydroxybutyl)-Nitrosamine-Induced Transitional Cell Carcinomas in the Urinary Bladder of Rats.** (Eng) Kunze, E. (Inst. Pathology, Univ. Gottingen, Gosslerstr. 10, D-3400 Gottingen, W. Germany); Schauer, A.; Schatt, S. *Z Krebsforsch* 87(2): 139-160; 1976.

The histogenesis of papillary and nonpapillary transitional cell carcinomas in the urinary bladder was studied morphologically and autoradiographically in 177 female Wistar rats given N-butyl-(4-hydroxybutyl)-nitrosamine (BBN; 20 mg/kg/day) in the drinking water. The animals were divided into four groups receiving BBN for 40, 80, 120, and 150 days, respectively. After a total induction time of 150, 200, and 250 days, animals from each group were sacrificed. The largest proportion of carcinomas developed by a malignant transformation of preexisting papillomas or their precursors, the papillary hyperplasias. The transition into a focally malignant growth occurred stepwise through different successive stages of transformation. Carcinoma in situ developed out of focal, sharply defined cellular atypia and progressed into circumscribed infiltrative growth. Of all the registered papillomas, 74.4% were transformed, indicating that papillomas are potentially highly malignant. The ³H-thymidine (³H-TdR) labeling index was determined in the transformation stages of papillomas and in well-differentiated invasive non-papillary transitional cell carcinomas after varying BBN exposure and induction times as well as after varying radioactive exposures. The ³H-TdR index was 4.2X higher in atypical urothelial areas (7.6%) and 7.5X higher in in situ carcinomas (14.3%) than in the surrounding benign papillomatous structures. The length of exposure and induction

time exercised no significant influence on the degree of proliferative activity. (46 refs.)

77-6262 **Morphology, Classification and Histogenesis of N-Butyl-N-(4-hydroxybutyl)-nitrosamine-Induced Carcinomas in the Urinary Bladder of Rats.** (Eng) Kunze, E. (Inst. Pathology, Univ. Gottingen, Gosslerstrasse 10, D-3400 Gottingen, W. Germany); Schauer, A. *Z Krebsforsch* 88(3): 273-289; 1977.

Experiments were conducted to determine whether the various histological types of carcinomas occurring in the human urinary bladder, their growth forms, and their biological behavior could be reproduced by n-butyl-n-(4-hydroxybutyl)nitrosamine (BBN) in rats. BBN, 20 mg/kg/day, was added to the drinking water of 177 female Wistar rats for 40-150 days. The animals were sacrificed after 150, 200, or 250 days. The carcinomas induced included all the types known to occur in man. They also occurred with the same frequency and growth patterns as those in man. Variably differentiated papillary and nonpapillary transitional cell carcinomas comprised 88.8% of the tumors registered; 5.1% were keratinized and nonkeratinized squamous cell carcinomas, 2.2% adenocarcinomas, 1.1% undifferentiated carcinomas, and 2.8% were mixed-type carcinomas with squamous cell and transitional cell differentiation. The adenocarcinomas originated from glandular metaplasia and the squamous cell carcinomas from squamous metaplasia within completely developed transitional cell carcinomas. Proliferative lesions such as von Brunn's nests, cystitis cystica, and cystitis glandularis were also induced. No evidence was found to substantiate the development of adenocarcinomas from these proliferative lesions or squamous cell carcinomas from squamous metaplasia of the otherwise unchanged urothelium. It is concluded that BBN is an excellent selective carcinogen that is able to induce the entire spectrum of bladder carcinomas naturally occurring in humans. (58 refs.)

77-6263 **Carcinogenic Effects of Diisopropanolnitrosamine in Sprague-Dawley Rats.** (Eng) Mohr, U. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, 3000 Hannover 61, Karl-Wiechert-Allee 9, W. Germany); Reznik, G.; Pour, P. *J Natl Cancer Inst* 58(2): 361-366; 1977.

A total of 120 Sprague-Dawley rats were divided into four groups and given sc injections of either 1/5 (I), 1/10 (II), 1/20 (III), 1/40 (IV) the LD50 of diisopropanolnitrosamine (DIPN; LD50, 7,125.5 mg/kg) once weekly for 20 wk. Following chronic treatment, rats of both sexes developed tumors of the nasal cavities, lungs, thyroid gland, esophagus,

liver, pancreas, and kidneys. Nasal cavity tumors were most frequent; they were multiple, and they originated from the nasoturbinals and maxilloturbinals or from the maxillary sinuses. There was a 36.4% incidence of nasal tumors in Group III and up to an 80% incidence of exo- and endoturbinal tumors in Groups III and IV. These neoplasms were either adenocarcinomas or squamous cell carcinomas. Most pulmonary neoplasms were squamous cell carcinomas. There was a 15.4% to 50% incidence of malignant thyroid gland tumors (adenocarcinomas) that occurred at almost the same rate in Groups I-III. There was a 78.6% incidence of liver neoplasms, including 25 angiosarcomas, 12 mixed-cell carcinomas, and 3 hepatocellular adenomas. All esophageal neoplasms were squamous cell papillomas. Only one pancreatic duct carcinoma was observed, and it occurred in a Group I rat. In a previous experiment with Syrian hamsters, a 100% incidence of pancreatic tumors was caused by DIPN. It was concluded that DIPN is a potent carcinogen that produces tumors after latency periods of only 23 wk for some adenomas and 26 wk for some adenocarcinomas. (16 refs.)

- 77-6264 **Effect of Di-isopropanolnitrosamine in European Hamsters.** (Eng) Reznik, G. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, D-3000 Hannover, W. Germany); Mohr, U. *Br J Cancer* 36(4): 479-486; 1977.

The effect of di-isopropanolnitrosamine (DIPN) on hibernating (Hi) and nonhibernating (NHi) European hamsters was examined. The NHi hamsters received weekly sc injections of 650, 325, 162.5 or 81.25 mg/kg DIPN for 25 wk. The Hi animals received either 650 or 81.25 mg/kg/wk for 25 wk. All animals receiving the highest dose died within 6 to 11 wk. Hi animals receiving the lowest dose died before the NHi animals on the same dose. Tumors were produced in the nasal cavity, trachea, lung, liver and pancreas with the main target organs being the anterior nasal cavity and liver. Only cholangiomas and cholangiocarcinomas were found in the liver. As early as 4 wk after initiation of treatment, changes were noted in the intrahepatic bile ducts and pancreatic ductal epithelium. Fourteen of the 144 treated hamsters developed pancreatic duct tumors; 2 of these were malignant. The tumorigenic response was lower in the Hi animals than in the NHi animals. These findings are compared with those in Syrian golden hamsters and Sprague-Dawley rats. (14 refs.)

- 77-6265 **Induction of Malignant Vascular Tumors of the Liver in Guinea Pigs Treated with 2,2'-Dihydroxy-di-n-propylnitrosamine.** (Eng) Rao, M. S. (Dept. Pathology, Northwestern Univ., Medical Sch., Ward Memorial Building, 303 E. Chicago Ave., Chicago, IL 60611); Reddy, J. K. *J Natl Cancer Inst* 58(2): 387-392; 1977.

Forty male random-bred guinea pigs were inoculated sc with

250 mg/kg (0.05 LD₅₀) 2,2'-dihydroxy-di-n-propylnitrosamine (DHPN) for 30 wk and then sacrificed at 40 wk. Of the 32 guinea pigs that survived > 20 wk, 23 developed angiosarcoma of the liver between 22 and 40 wk. Metastatic lesions were seen in the lungs, spleen, and peripancreatic lymph nodes of eight animals. Other tumors that resulted included 1 hepatocellular carcinoma, 1 cholangiocarcinoma, 1 case of chronic myeloid leukemia, 2 acinar cell pancreatic adenomas, and small pulmonary alveolar adenomas in one animal. Numerous multiloculated cysts that often distorted the lobular architecture of the liver occurred in 78% of the guinea pigs. There was also a high incidence of megalocytic changes of the hepatic cells; ie, intranuclear inclusions, peliosis hepatis, and cholangiomatous lesions. (26 refs.)

- 77-6266 **Demonstration of Nitrosamines in Human Urine: Preliminary Observations on a Possible Etiology for Bladder Cancer in Association with Chronic Urinary Tract Infections.** (Eng.) Hicks, R. M. (Sch. Pathology, Middlesex Hosp. Medical Sch., London W1P 7LD, England); Walters, C. L.; Elsebai, I.; El Aasser, A. B.; El Merzabani, M.; Gough, T. A. *Proc R Soc Med* 70(6): 413-417; 1977.

A study was made of the nitrosamine content of urines from three groups of patients: (1) 10 English patients with neoplastic bladder disease, (2) 11 English hemiplegic and paraplegic patients, and (3) 5 Egyptian patients with neoplastic bladder disease superimposed on bilharziasis of the urinary bladder. Total amounts of volatile plus nonvolatile extractable nitrosamine in dichloromethane extracts of the urines were determined by a method specific for N-nitroso compounds. The volatile nitrosamines were identified further by gas chromatography coupled with high-resolution mass spectrometry. From the first group, the only urine in which a trace amount of nitrosamine was detectable was from a woman with a large bladder tumor and a heavy urinary infection. Significant amounts of nitrosamines were detected in the urine of three patients in the second group who also had active bacterial infections of the bladder; none of these patients had neoplastic bladder disease. Nitrosamines were found in the urine from three of the Egyptian patients. Although nitrosatable precursors were available in considerable quantities in both Egyptian and English individuals, even when bacteria were present, the amounts of nitrosamines actually formed were far greater in the Egyptian than in the English subjects, suggesting that some other unidentified factor has a controlling influence on the nitrosamine production. (17 refs.)

- 77-6267 **Nitrosamines as Respiratory Carcinogens: Experimental Studies (Meeting Abstract).** (Eng) Stenback, F. (Eppley Inst., Univ. Nebraska, Omaha, NB 68105). In: *Fourth Meeting of the European Association for*

Cancer Research, 13th-15th September, 1977. International Agency for Research on Cancer. (Lyon, France): p. 68; 1977. (no refs.)

77-6268 Quantum-Mechanical Investigations of Unstable Intermediates Relevant to the Mechanism of Chemical Carcinogenesis by N-Alkyl-N-nitrosamines. (Eng) Thomson, C. (Dept. Chemistry, Univ. St. Andrews, St. Andrews, Scotland); Provan, D.; Clark, S. *Int J Quantum Chem Quantum Biol Symp* (4): 205-215; 1977.

Ab initio LCAO-MO-SCF calculations of the transformation of nitroxylamide to hydroxydiimide and of monomethylnitrosamine to the corresponding diazohydroxide are reported. A large barrier was obtained in both cases but this was lowered by 10% when the molecules were allowed to interact with a single water molecule. It was concluded that the diazohydroxide more likely arises from the α -hydroxy derivative than from the monomethylnitrosamine. The relevance of these investigations to carcinogenesis by N-nitrosamines is discussed. (39 refs.)

77-6269 Carcinogenic Effect of Di-Nitrosopiperazine Formed from Triforine (Meeting Abstract). (Eng) Borzsonyi, M. (Natl. Inst. Hygiene, 1966 H-Budapest, Hungary); Pinter, A.; Nadasdi, L. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977. International Agency for Research on Cancer. (Lyon, France): p. 65; 1977. (no refs.)*

77-6270 Induction of Pancreatic Duct Carcinomas in the Syrian Hamster with 2,6-Dimethylnitrosomorpholine. (Eng) Mohr, U. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, 3000 Hannover 61, Karl-Wiechert-Allee 9, W. Germany); Reznik, G.; Emminger, E.; Lijinsky, W. *J Natl Cancer Inst* 58(2): 429-432; 1977.

Four groups of 15 male and 15 female 8-wk-old Syrian hamsters were given intragastric 2,6-dimethylnitrosomorpholine (DMNM) once weekly for life at a dose of either 1/5, 1/10, 1/20, or 1/40 of the LD₅₀ (367 mg/kg). As early as 30 wk after the beginning of treatment, animals in the highest dosage group died with macroscopically visible pancreatic tumors. The max incidence of pancreatic tumors in the various groups was 71%. The neoplasms were generalized throughout the pancreas, measured up to 40 mm in diameter, and often infiltrated into the stomach, liver, spleen, and intestines. Histologically, they were adenomas and adenocarcinomas of the pancreatic ducts. Some metastasis to the lungs was observed. Adenomas and carcinomas also developed in the gall bladder, intrahepatic part of the bile duct, nasal cavities, larynx, tracheas, and kidneys. Respiratory tract primary tu-

mors included papillomas, polyps, adenomas, adenocarcinomas, and squamous cell carcinomas. The incidence ranged between 0% and 60% in the various groups. (8 refs.)

77-6271 Early Changes of Glandular Stomach in Wistar Rats Ingesting N-Methyl-N'-Nitro-N-Nitrosoguanidine (MNNG): With Special Reference to Light Microscopic, Electron Microscopic, and Enzyme Histochemical Study of the Regenerating Epithelium Induced by MNNG. (Eng) Kobori, O. (Univ. Tokyo, Faculty Medicine, Dept. Surgery, 7-3 Hongo, Bunkyo-ku, Tokyo, Japan); Gedigk, P.; Totovic, V. *Z Krebsforsch* 87(2): 127-138; 1976.

Early mucosal changes of the glandular stomach in male Wistar rats ingesting N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were studied to elucidate the positional and chronological relationship between the expected regenerative changes and the succeeding adenomatous change or carcinoma. Rats were given MNNG (80 μ g/ml) in the drinking water ad libitum for 31 wk; from the 3rd to 35th wk, 2-3 rats were killed every other wk. The stomach was removed and studied by light and electron microscopy and by enzyme histochemical techniques. Localized erosions appeared in the 5th wk and were observed until about the 20th wk. These changes were always located near the midpoint of the lesser curvature. Comparison of the MNNG-induced regenerative epithelial cells with the neck cells of normal gastric epithelium and with mechanically induced regenerative epithelial cells showed almost complete identity. From about the 20th wk, two cases showing ectopic gland, four adenomatous changes, two early carcinomas, and five invasive carcinomas were found. These lesions were all located on the lesser curvature near its midpoint, i.e. exactly the same area where the early erosions were observed. Both the identical localization of these lesions and the evident chronological sequence of their development suggest that one lesion is followed inevitably by the other, leading finally to malignant growth. (24 refs.)

77-6272 Banding Pattern Analysis of Initial Structural Chromosome Alterations Induced by N-Methyl-N'-nitro-N-nitrosoguanidine in Syrian Hamster Cells. (Eng) DiPaolo, J. A. (Somatic Cell Genetics Section, Biology Branch, Carcinogenesis Program, Div. Cancer Cause and Prevention, NCI, Bethesda, MD 20014); Popescu, N. C. *Mutat Res* 44(3): 359-368; 1977.

Syrian hamster embryo (LVG: LAK random-bred strain) cultures were exposed to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG; 0.5 μ g/ml culture medium) for 5, 13, and 28 hr and examined for chromosome aberrations. No chromosome or chromosome segment of the Syrian hamster gene complement was preferentially vulnerable to the effects of MNNG, although chromosomes belonging to the larger groups were affected more often. G-band analysis

showed that 80% of the lesions occurred in negative bands, 9% at the centromere, and 3% on unbanded heterochromatic regions; for 8%, the precise location could not be pinpointed. The number of chromatid exchanges per 100 cells was approx 8%-9%. Out of 100 interchanges analyzed, 91 involved the relatively longest chromosomes. There was no correlation between frequency of individual chromosome breaks and concomitant involvement in chromatid exchanges. The X and Y chromosomes and an autosome (E 20) did not rejoin with chromatids of other chromosomes. The asymmetrical type of exchange predominated with MNNG, all being of the U form except for one X form. Complete and incomplete exchanges were roughly equal in number. The question that remains is whether these early chromosomal alterations are determinants of transformation and malignancy or whether they are reflections of MNNG toxicity. (38 refs.)

- 77-6273 Inhibition by Retinol and Butylated Hydroxyanisole of Carcinogen-mediated Increases in Guanylate Cyclase Activity and Guanosine 3':5'-Monophosphate Accumulation.** (Eng) Craven, P. A. (Dept. Medicine, Veterans Admin. Hosp., Drive C, Pittsburgh, PA 15240); DeRubertis, F. R. *Cancer Res* 37(11): 4088-4097; 1977.

Retinol and butylated hydroxyanisole (BuHA) and their analogs, retinoic acid and butylated hydroxytoluene, suppressed the ability of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) to stimulate soluble guanylate cyclase (GC) activity and cyclic guanosine 3':5-monophosphate (cGMP) accumulation in Sprague-Dawley rat liver and colonic mucosa. Optimal inhibition of MNNG-responsive soluble hepatic GC activity was observed after preincubation of the tissue with 1 mM retinol (58% decrease), 3 mM BuHA (80%), 3 mM retinoic acid (30%), and 3 mM butylated hydroxytoluene (21%). In contrast, preincubation of tissue with up to 5 mM of these agents had no effect on basal GC activity measured in the absence of MNNG. The inhibitory effects of retinol and BuHA were greatest when they were added to the tissue prior to the addition of MNNG. The inhibitory effects of these agents could not be attributed to alterations in the divalent cation requirements of soluble hepatic GC activity or to direct chemical interactions leading to loss of the nitroso group from MNNG. The action of retinol and BuHA in suppressing the responsiveness of hepatic GC to several carcinogens (MNNG, N-methylnitrosourea, hydrazine, and 4-nitroquinoline 1-oxide) is selective relative to their effects on the responsiveness of adenylate cyclase. The suppression of the carcinogen activation of GC could be involved in the expression of the anticarcinogenic properties of the two compounds. (59 refs.)

- 77-6274 Carcinogenic Effect of N-Nitroso Compounds Formed In Vivo from Dodecylguanidine and Methylguanidine on Pregnant Mice and Their Offspring.** (Hun) Borzsonyi, M. (Natl. Inst. Public Health, Budapest,

Hungary); Pinter, A.; Surjan, A.; Torok, G.; Sajgo, M. *Magy Onkol* 21(3): 197-206; 1977.

Dodecylguanidine acetate (DG, 6 and 40 mg/kg) and methylguanidine (MG, 40 mg/kg) were administered intragastically to Swiss mice in the last week of pregnancy. Simultaneously, the mice received drinking water containing 0.05% sodium nitrite. Tumors, mostly malignant lymphomas, pulmonary adenomas, and hepatomas, developed in 30%-70% of the mothers (4-5 mo after treatment) and their offspring (6-7 mo after delivery). The frequency of spontaneous tumors (lymphomas) in the same strain was 6%; these tumors developed after 10 mo. These results confirm the carcinogenicity of the N-nitroso compounds formed in vivo from DG and MG in the presence of nitrite. A- and C-type RNA virus particles were detected in the lymphomas. No increase in tumor incidence in the mothers and the F₁ generation occurred following treatment with DG alone. (23 refs.)

- 77-6275 Guanosine-Methyldiazonium Ion Reaction: Variation of Methylation Product Patterns with Reaction Variables.** (Eng) Sullivan, J. P. (Dept. Chemistry, Univ. Louisville, Louisville, KY 40208); Wong, J. L. *Biochem Biophys Acta* 479(1): 1-15; 1977.

The effects of reaction variables on the methylation of guanosine by methyldiazonium ion were studied by high-pressure liquid chromatography and proton magnetic resonance spectroscopy. The methylation product patterns of the reaction were sensitive to the effects of medium, polarity, temperature, salt addition, stoichiometry, and pH. The percent yields of methylation at the nitrogen, oxygen, and carbon sites were determined, achieving material balance of > 95%. The major products were 1-methylguanosine, O⁶-methylguanosine, and 7-methylguanosine. The 7-methylguanosine yields were adjusted for 1,7-diethylguanosine, a secondary methylation product, as well as for ring-opened products from 7-methylguanosine and 1,7-dimethylguanosine. The different methylation patterns plotted as O:N ratios of yields of the three major products, eg, the O⁶:N⁷ product ratios ranging from a high of 1.6 (methanol/ether medium) to a low of 0.2-0.0 (aqueous), indicate that the methylation product pattern of the guanine residue in a nucleic acid will also be dictated by the reaction conditions of the methyldiazonium ion attack. (30 refs.)

- 77-6276 Long-term Persistence of O⁶-Methylguanine in Rat Brain DNA.** (Eng) Kleihues, P. (Pathologisches Institut der Universität, Abteilung Neuropathologie, 78 Freiburg i. Br., W. Germany); Bucheler, J. *Nature* 269(5629): 625-626; 1977.

O⁶-methylguanine persisted in DNA of various organs of adult, female BD-IX rats that received a single dose of N-methyl-N-nitrosourea (MNU; 10 mg/kg, iv). Excision from

hepatic DNA was most rapid, with O⁶-methylguanine concentrations below the detectable level within 7 days; in lung and kidney DNA, excision was accomplished by 28 and 84 days, respectively. However, at 184 days, 25% of the initial concentration was present in cerebral DNA. The pertinence of this data to the induction of glial tumors by MNU and related carcinogens is discussed. (15 refs.)

- 77-6277 **Hepatocarcinogenic Effects of N-Nitroso-N-methylurea in Guinea Pigs.** (Eng) Yoshida, A. (Occupational and Environmental Medicine, Sch. Public Health, Univ. Illinois at Medical Center, Chicago, IL 60680); Iqbal, Z. M.; Epstein, S. S. *Cancer Res* 37(11): 4043-4048; 1977.

The intragastric administration of N-nitroso-N-methylurea (NMU; 7.5 mg/kg weekly for 15 wk, then twice weekly for 15 wk) to 44 strain 13 male guinea pigs resulted in 61% and 100% mortality by 30 and 40 wk, respectively. Among the 18 animals surviving 30 wk, there were six hepatic neoplasms (4 angiosarcomas and 2 cholangiocarcinomas) and six generalized lymphoblastic lymphomas. These results, together with a gradual wt loss, demonstrate the hepatotoxic and hepatocarcinogenic effects of MNU in the guinea pig. (25 refs.)

- 77-6278 **Structural Changes Induced by N-Nitrosomethylurea in Bacterial Cell DNA.** (Rus) Vasil'eva, S. V. (Inst. Chemical Physics, USSR Acad. Sciences, Moscow, USSR); Davnichenko, L. S.; Kondrat'ev, Iu. S.; Skavronskaja, A. G. *Dokl Akad Nauk SSSR* 235(5): 1186-1188; 1977.

In *Escherichia coli* K12 DNA, N-nitrosomethylurea caused single-strand breaks at concentrations of 0.005-0.1 M and double-strand breaks at 0.01-0.1 M. (14 refs.)

- 77-6279 **Introduction to the L 5222 Leukaemia.** (Eng) Haemmerli, G. (Div. Cancer Res., Inst. Pathology, Univ. Zurich, Birchstrasse 95, 8050 Zurich, Switzerland); Felix, H. *Leuk Res* 1(2/3): 79-83; 1977.

The transplantable L 5222 leukemia, induced by ethylnitrosourea (single iv injection of 200 mg/kg) in a BD IX rat, is described briefly. L 5222 is propagated by ip injection of 5×10^7 tumor cells. The animals die around day 7 with widely disseminated leukemia. Its cytochemistry, DNA content, chromosome analysis, and ultrastructural cytology are reported. The findings lead to the conclusion that L 5222 is undifferentiated and unclassifiable leukemia. (17 refs.)

- 77-6280 **The Effect of N-Nitrosoethylurea and Postnatal Irradiation on Transplacental Blastomogenesis in Mice.** (Rus) Napalkov, N. P. (Lab. Experimental Tumors, N. N. Petrov Scientific Res. Inst. Oncology, USSR Ministry

Public Health, Leningrad, USSR); Tomatis, L.; Likhachev, A. Ia.; Kolodin, V. I. *Vopr Onkol* 23(5): 66-70; 1977.

Transplacental exposure of BALB/c mice to 2 mg/kg nitrosoethylurea (NEU) resulted in the same frequency of tumors as exposure to 20 mg/kg. However, with the former dose, lung tumor development was prolonged. Postnatal irradiation with 150 R increased the incidence of lung adenomas and ovarian tumors in female mice exposed in embryogenesis to 2 mg/kg NEU; male mice showed a delayed development of tumors. In mice exposed to 20 mg/kg NEU, postnatal irradiation with 150 R resulted in lung adenocarcinomas; other tumors were not noted. (7 refs.)

- 77-6281 **A Correlative Study on the Genetic Damage Induced by Chemical Mutagens in Bone Marrow and Spermatogonia of Mice. III. 1, 3-Bis(2-chloroethyl)-3-nitrosourea (BCNU).** (Eng.) Bates, A. D. (Dept. Radiation Genetics and Chemical Mutagenesis, Sylvius Labs., Wassenaarseweg 72, State Univ. Leiden, Leiden, The Netherlands); Natarajan, A. T.; de Vogel, N.; Meijers, M. *Mutat Res* 44(1): 87-95; 1977.

The genetic effects of 1,3-bis(2-chloroethyl)-3-nitrosourea (BCNU) on mice in vivo and of BCNU and 1-(2-chloroethyl)-3-nitrosoureaethanol (CNU-ethanol) on mouse cells in vitro were examined. BCNU was given ip to 12- to 18-wk-old CBA male mice as a single injection of 1.45-81.45 mg/kg. Some mice were killed after 24-48 hr for study of bone marrow cells and spermatogonia and others were killed after 8 wk for spermatocyte analysis. For the in vitro experiment, aneuploid lung fibroblasts from the tobacco mouse were treated for 1 hr with either BCNU or CNU-ethanol at 1, 3, and 10 μ g/ml. Cytogenetic damage induced by BCNU was evaluated by determining the frequencies of micronuclei in polychromatic RBC of bone marrow, chromatid aberrations in bone and in spermatogonia, and reciprocal translocations induced in spermatogonia and scored in spermatocytes. The order of sensitivity was micronuclei > chromatid aberrations in bone marrow > aberrations in spermatogonia > translocations in spermatocytes. When the effect of concentration was considered, there was no correlation among the four parameters. On the basis of the present data, it is not justified to conclude that information on induced frequencies of micronuclei can be used to predict frequencies of chromatid aberrations in bone marrow cells. Both BCNU and CNU-ethanol induced significant amounts of chromatid aberrations in the mouse lung fibroblasts. Except for the lowest concentrations tested, BCNU was more effective than CNU-ethanol in inducing aberrations of the interchange type. A comparison of the in vivo results for BCNU with published results of an in vivo CNU-ethanol study indicated that BCNU had a similar or a lesser cytogenetic effect than did CNU-ethanol. (4 refs.)

- 77-6282 **A Comparison of the Distribution, Metabolism and Excretion of Ethylenethiourea in the Pregnant Mouse and Rat.** (Eng) Ruddick, J. A. (Food Directorate, Health Protection Branch, Tunney's Pasture, Ottawa,

Ontario K1A 0L2, Canada); Newsome, W. H.; Iverson, F. *Teratology* 16(2): 159-162; 1977.

Pregnant Swiss White mice and Wistar rats were treated by stomach intubation on day 15 of gestation with 240 mg/kg of ethylenethiourea (ETU) made up in part with radiolabeled ETU. Animals were sacrificed at various times posttreatment, and maternal tissues, fetus, urine, and feces were collected for radioactivity determinations. Maternal and fetal tissue levels of ETU were similar at 3 hr posttreatment; thereafter, the mouse (mother and fetus) showed much less ETU than the rat. The calculated half-life of ETU and its metabolites in the maternal blood was 9.4 and 5.5 hr for the rat and mouse, respectively. Analysis of the urine by thin-layer chromatography and radiochromatography revealed that the mouse and rat metabolized ETU by different pathways. Furthermore, the mouse is able to metabolize ETU to a greater extent than the rat. (13 refs.)

77-6283 Sensitivity Differences of Hamsters and Rats to Long-term Administration of Ethylene Thiourea. (Fre) Gak, J. C. (Centre de Recherches Toxicologiques, Faculté des Sciences Pharmaceutiques et Biologiques de Paris-Luxembourg, 4, Avenue de l'Observatoire, 75006 Paris, France); Graillot, C.; Truhaut, R. *Eur J Toxicol* 9(5): 303-312; 1977.

The carcinogenicity of ethylene thiourea (ETU) was investigated in rats and hamsters at concentrations of 5, 17, 60, and 200 mg/kg. ETU resulted in hypercholesterolemia in both species when administered at 5 mg/kg. Thyroid impairment was the predominant pathology in the rat; hepatic impairment, in the hamster. ETU was not carcinogenic in hamsters even at the highest dosage level. It was carcinogenic, however, in male rats above 60 mg/kg and in females at 200 mg/kg. Changes in body wt, food consumption, and hepatic enzymatic activities (alkaline phosphatase, glutamic pyruvate transaminase, and glucose-6-phosphate dehydrogenase) are reported. (11 refs.)

77-6284 Pulmotropic Carcinogenic Activity of N-Methyl-N-nitrosopropionamide. (Eng) Stekar, J. (Dept. Pharmacology, Asta-Werke AG, D-4800 Bielefeld 14, W. Germany). *Eur J Cancer* 13(10): 1183-1189; 1977.

When injected iv into BD rats at a dose of 2 mg/kg/wk for 31 wk, N-methyl-N-nitrosopropionamide (MNPA) selectively induced lung tumors in a high yield. Moreover, like the well-known pulmonary carcinogen N-methyl-N-nitrosourea, MNPA reacted with cysteine to yield elementary nitrogen. On the other hand, N-methyl-N-nitrosourea, a powerful neurotropic carcinogen, does not react with cysteine nor induce lung cancer. It is concluded that reaction with cysteine under concomitant N₂-liberation might be a characteristic feature of lung cancer-inducing nitrosamides. (16 refs.)

77-6285 Transplantable Pancreatic Carcinoma of the Rat. (Eng) Reddy, J. K. (Dept. Pathology, Medical Sch., Northwestern Univ., Chicago, IL 60611); Rao, M. S. *Science* 198(4312): 78-80; 1977.

A transplantable pancreatic carcinoma developed in a male Fischer 344 rat that was fed 0.1% nafenopin 2-methyl-2-[p-(1,2,3,4-tetrahydro-1-naphthyl)phenoxy] propionic acid for 10 mo. The tumor cells contained numerous zymogen granules, and the endoplasmic reticulum and Golgi apparatus were prominent. The tumor was capable of producing amylase and lipase. It is suggested that it would be a useful method for chemotherapy and immunotherapy experiments and for investigating the synthesis and transport of zymogen proteins in neoplastic cells. (12 refs.)

77-6286 Failure of the N-oxidized Metabolites of Some Carcinogenic Amines to Induce Tumors in Normal and Wounded Rat Skin. (Eng) Brill, E. (Dept. Pharmacology, Univ. Miami Sch. Medicine, Miami, FL 33152); Radomski, J. L.; MacDonald, W. E. *Res Commun Chem Pathol Pharmacol* 18(2): 353-360; 1977.

The skin of Osborne-Mendel and Sprague-Dawley rats was treated by repeated topical applications of 1.5 mg of 1-naphthylamine, 2-naphthylamine, N-1-naphthylhydroxylamine, N-2-naphthylhydroxylamine, 1-nitrosonaphthalene, and 2-nitrosonaphthalene. In addition, the possibility of enhancing the susceptibility of the skin to tumor induction by periodic wounding at the site of compound application was investigated in the Sprague-Dawley rats. The compounds were applied twice weekly for 52 wk, and the animals were observed for an additional year. None of the compounds induced skin tumors, although some of the N-oxidized arylamine metabolites produced a few systemic tumors, primarily hepatomas and lymphosarcomas, in the Osborne-Mendel rats. Skin wounding did not increase tissue sensitivity to the carcinogenic effect of the test compounds. (13 refs.)

77-6287 Differential Sensitivity of Xeroderma Pigmentosum Cells of Different Repair Capacities Towards the Chromosome Breaking Action of Carcinogens and Mutagens. (Eng) San, R. H. (Cancer Res. Center, Univ. British Columbia, Vancouver, Canada); Stich, W.; Stich, H. F. *Int J Cancer* 20(2): 181-187; 1977.

A study was conducted to determine a possible quantitative relationship between different levels of DNA repair deficiency of xeroderma pigmentosum (XP) cells and different sensitivities to the chromosome-breaking action of the carcinogens 4-nitroquinoline 1-oxide (4NQO), N-acetoxy-2-acetylaminofluorene (N-acetoxy-2-AAF) and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and to the mutagen daunomycin. Cultured fibroblasts were obtained from four unrelated XP patients (XP-K, XP-C, XP-E, and XP-H). After treatment with 4NQO (5×10^{-7} M) and N-acetoxy-2-AAF (1×10^{-5} M) the frequency of chromosome aberrations increased in

the order XP-K > XP-C > XP-E > XP-H, with a decreasing DNA repair capacity in the order of XP-K > XP-C > XP-E > XP-H. MNNG (2.5×10^{-5} M) induced these reactions in the four XP cell types at levels comparable to those in fibroblasts of nonafflicted persons. Daunomycin induced similar frequencies of chromosome aberrations in the XP cells and controls, but it did not trigger DNA repair synthesis. Heterozygous XP cells from the parents of the four XP patients responded similarly to control cells to the four agents. The results show that the increased sensitivity of XP cells manifests itself only in tissues or organs that are exposed to a physical or chemical carcinogen. (26 refs.)

77-6288 Excision of 4-Nitroquinoline 1-Oxide Damage and Transformation in Mouse Cells. (Eng) Ikenaga, M. (Dept. Fundamental Radiology, Faculty Medicine, Osaka Univ., Kita-ku, Osaka 530, Japan); Kakunaga, T. *Cancer Res* 37(10): 3672-3678; 1977.

Cell transformation by 4-nitroquinoline 1-oxide (4NQO), the effect of hydroxyurea (HU) on transformation frequency, and the excision repair of 4NQO lesions were studied in mouse A31-714 cells, a BALB/3T3 subclone. When present in the medium for 12 and 24 hr after 4NQO treatment, HU reduced transformation frequency to 28% and 6%, respectively, of that in cells incubated without HU. The effect of HU resembled that of density inhibition, which also prevented the production of transformed foci by 4NQO. Excision repair of the 4NQO lesions was measured by autoradiography of ^3H -thymidine incorporation or by chromatographic analysis of the four kinds of 4NQO-purine adducts remaining in DNA after posttreatment incubation. Excision repair was rapid in nondividing cells and unaffected by the presence of HU in the medium. The fractions of repaired lesions, estimated from excision and repair synthesis experiments, were about 50% after 12 hr and 65%-90% after 24 hr, which indicates a correlation in time between DNA repair and cell transformation. The results demonstrate that mouse cells excise 4NQO-purine adducts by a repair system similar to that involved in the repair of UV-induced pyrimidine dimers in human cells and that the unexcised fractions of these adducts are the major cause of cell transformation by 4NQO. (29 refs.)

77-6289 Isolation and Cultivation of Cells from Carageenan-induced Granulomas of the Mouse (Meeting Abstract). (Eng) Bonney, R. J. (Merck Inst. for Therapeutic Res., Rahway, NJ 07065); Richardson, T. G.; Dahlgren, M. E.; Davies, P. *In Vitro* 13(3): 174-175; 1977. (no refs.)

77-6290 A 2-Year Feeding Study of Instant Coffees in Rats. II. Incidence and Types of Neoplasms. (Eng) Wurzner, H. P. (Nestle Products Technical Assistance Co., Ltd., Biological Lab., CH-1350 Orbe, Switzerland); Lindstrom, E.; Vuataz, L.; Luginbuhl, H. *Food Cosmet Toxicol* 15(4): 289-296; 1977.

Various regular and decaffeinated coffees were given to Sprague-Dawley rats in max tolerated dose levels of 6% in a standard commercial diet ad lib. for 2 yr in order to investigate the effects of long-term administration and such variables as extraction rates, decaffeination techniques, and industrial drying techniques. Rats were divided into a control group and 13 experimental groups, including 7 given coffees from which caffeine had been extracted with methylene chloride. The av daily intake of coffee (calculated after the first 4 wk) was 2.9 g/kg for males and 3.5 g/kg for females. Ten male and ten female rats from each group were randomly selected for autopsy at 3 and at 12 mo, and the remaining survivors killed at 24 mo. Of neoplasms tabulated, 85% were embryonal nephromas, lymphosarcomas, mammary fibroadenomas, or adrenal adenomas. In three groups receiving high levels of caffeine (approx 347-370 mg/kg av daily intake in either regular coffee or decaffeinated coffee plus caffeine), the incidence of neoplasms was lowered significantly. None of the other variables had a significant effect on incidence of neoplasms as compared to controls. It is concluded that decaffeination with methylene chloride does not increase the risk of neoplasm induction. (28 refs.)

77-6291 Sister Chromatid Exchange and Chromatid Interchange as Possible Manifestation of Different DNA Repair Processes. (Eng) Sasaki, M. S. (Dept. Cytogenetics, Medical Res. Inst., Tokyo Medical and Dental Univ., Yushima, Bunkyo-ku, Tokyo 113, Japan). *Nature* 269(5629): 623-625; 1977.

The effects of caffeine (200 $\mu\text{g}/\text{ml}$) and cycloheximide (0.1 $\mu\text{g}/\text{ml}$) on sister chromatid exchange (SCE) and chromatid interchange (CI) during endoreduplication of cultured human embryonic skin fibroblasts were studied. After 24 hr, caffeine reduced intradiplod-CIs (IDCIs) but increased single SCEs, whereas cycloheximide had no effect on IDCIs but suppressed single SCEs. These data demonstrate a two-step, replication-mediated DNA repair mechanism manifested cytologically by SCE and CI, which are independent events. (29 refs.)

77-6292 The Effect of Mitomycin on the Fertility and the Induction of Meiotic Chromosome Rearrangements in Mice and Their First Generation Progeny. (Eng) Savkovic, N. (Lab. Radiobiology, "Boris Kidric", Inst. Nuclear Sciences, Belgrade, Yugoslavia); Green, S.; Pecevski, J.; Maric, N. *Can J Genet Cytol* 19(3): 387-393; 1977.

The effect of chronic mitomycin C administration (0.5 or 0.1 mg/kg/day for 8 wk) on fertility and induction of chromosomal translocations in male in C_3H mice and the F_1 males was examined. No chromosomal translocations were found in diakinesis-metaphase I of meiosis in the treated males; all males were fertile but not all females were pregnant. The testes of sterile, semisterile and fertile F_1 males showed that they could not be identified as heterozygous translocation carriers. (31 refs.)

- 77-6293 **DNA Repair after Use of Therapeutic Drugs and UV Damage.** (Eng) Perocco, P. (Istituto di Pathologia Generale, Università di Bologna, I-40126 Bologna, Italy); Rocchi, P.; Nanni, P.; Arfellini, G.; Prodi, G. *IRCS Med Sci: Cancer* 5(10): 505; 1977.

DNA repair was investigated following treatment of Wistar rat spleen cells with varying concentrations of 5-fluorouracil, methotrexate, 6-mercaptopurine, mitomycin C, daunorubicin (DNR), and UV light (singly and in drug-UV combinations) in the presence or absence of 5mM hydroxyurea as inhibitor of scheduled DNA synthesis. Repair of drug-induced DNA damage proceeded without change from 4 to 24 hr of culture. Repair was additive for UV-drug damage except with DNR at max dose, possibly explained by the high toxicity of this drug. (3 refs.)

- 77-6294 **Transformation of Rat Embryo Cells by Methotrexate (Meeting Abstract).** (Eng) Chlopkiewicz, B. (Inst. for Drug Res., Warsaw, Poland); Rossowski, W.; Koziorowska, J. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 79; 1977. (no refs.)

- 77-6295 **Bioassay Program for Carcinogenic Hazards of Cancer Chemotherapeutic Agents.** (Eng) Weisburger, E. K. (Building 37, Room 3B27, NCI, Bethesda, MD 20014). *Cancer [Suppl]* 40(4): 1935-1949; 1977.

Forty drugs or combinations of drugs used in the treatment of neoplastic diseases were tested for possible carcinogenicity in Swiss mice and Sprague-Dawley rats. Each compound was injected ip three times weekly for 6 mo at two doses: the max tolerated dose and one-half that level; 25 males and 25 females of each species received each dose, for a total of 200 animals. 4(5)-(3,3-Dimethyl-1-triazeno)imidazole-5(4)-carboxamide was the most active carcinogen, both in increasing tumor incidence and decreasing the time of tumor appearance. Compounds that were fairly active were procarbazine, melphalan, uracil mustard, streptozotocin, and 6-mercaptopurine. The other compounds showed little or no evidence of carcinogenicity. The carcinogenicity of the drug combinations was generally less than that of the individual components. (21 refs.)

- 77-6296 **Effects of Microbial Activity on Aquatic Pollutants.** (Eng) Voll, M. J. (Dept. Microbiology, Univ. Maryland, College Park, MD 20742); Isbister, J.; Isaki, L.; McCommas, M.; Colwell, R. R. *Ann NY Acad Sci* 298: 104-110; 1977.

Water and sediment samples from a heavily oil polluted area of the Chesapeake Bay were analyzed for mutagenicity by the Ames test. Potential mutagens and/or carcinogens were not detected in the microbial degradation products of these oil

extracts. Mutagenic substances may be present, but at concentrations below the detection level of the assay. (20 refs.)

- 77-6297 **Bile Acids: Co-mutagenic Activity in the Salmonella-Mammalian-Microsome Mutagenicity Test: Brief Communication.** (Eng) Silverman, S. J. (Dept. Biology, Hood Coll., Frederick, MD 21701); Andrews, A. W. *J Natl Cancer Inst* 59(5): 1557-1559; 1977.

None of the 30 bile acids tested for carcinogenicity in the Salmonella-mammalian microsome test were carcinogenic. However, when lithocholic acid or one of its conjugates was tested with suboptimal amounts of 2-aminoanthracene and a phenobarbital-stimulated homogenate, rat liver comutagenesis was observed in Salmonella strain TA1538. The mechanism of this enhancement is not known. (15 refs.)

- 77-6298 **Explant Culture of Rat Colon: A Model System for Studying Metabolism of Chemical Carcinogens (Meeting Abstract).** (Eng) Autrup, H. (Human Tissue Studies Section, Exp. Pathology Br., Carcinogenesis, NCI, Bethesda, MD 20014); Harris, C. C.; Stoner, G. D.; Fugaro, S. *In Vitro* 13(3): 192; 1977. (no refs.)

See also:

*(Rev.): 77-6001, 77-6002, 77-6003, 77-6004, 77-6005
77-6006, 77-6007, 77-6008, 77-6009, 77-6010
77-6011, 77-6012, 77-6013, 77-6014, 77-6015
77-6016, 77-6017, 77-6018, 77-6019, 77-6020
77-6021, 77-6022, 77-6023, 77-6024, 77-6025
77-6026, 77-6027, 77-6028, 77-6029, 77-6030
77-6031, 77-6032, 77-6033, 77-6034, 77-6035
77-6036, 77-6037, 77-6038, 77-6039, 77-6040
77-6041, 77-6042, 77-6043, 77-6044, 77-6045
77-6046, 77-6047, 77-6048, 77-6049, 77-6050
77-6051, 77-6052, 77-6053, 77-6054, 77-6055
77-6056, 77-6057, 77-6058, 77-6059, 77-6060
77-6061, 77-6062, 77-6063, 77-6064, 77-6065
77-6066, 77-6067, 77-6068, 77-6069, 77-6070
77-6071, 77-6072, 77-6073, 77-6076, 77-6100
77-6104, 77-6111, 77-6113, 77-6114, 77-6116
77-6121, 77-6123, 77-6125.

*(Phys.): 77-6303, 77-6306.

*(Viral): 77-6340, 77-6359.

*(Immun.): 77-6444, 77-6445, 77-6447, 77-6448, 77-6451
77-6456, 77-6457, 77-6459, 77-6461, 77-6465
77-6481, 77-6490, 77-6491, 77-6492, 77-6493
77-6494.

*(Path.): 77-6510, 77-6511, 77-6513, 77-6528, 77-6529
77-6553, 77-6566, 77-6568.

*(Epid.-Biom.): 77-6577, 77-6578, 77-6579, 77-6583, 77-6584
77-6585, 77-6586.

PHYSICAL CARCINOGENESIS

7-6299 **Estimation of the Protective Action of Prussian Blue, Sodium Alginate, and Calcium Phosphate against Tumor Induction by Single and Chronic Exposure to Strontium-90 plus Cesium-137.** (Rus) Danetskaia, E. V. Res. Inst. Radiation Hygiene, RSFSR Ministry Health, Leningrad, USSR; Lavrent'ev, L. N.; Zapol'skaia, N. A.; Teplykh, L. A. *Vopr Onkol* 23(6): 57-61; 1977.

The protective action of Prussian Blue (50 mg/day, po), sodium alginate (800 mg/day, po), and calcium phosphate (258 mg/day, po) against ^{90}Sr and ^{137}Cs in terms of tumor induction rate and absorbed dose, was studied in female albino rats. The rats were fed a single dose of ^{90}Sr (100 μCi) + ^{137}Cs (400 μCi) or daily doses of ^{90}Sr (0.8 μCi) + ^{137}Cs (2 μCi) until death. One group of animals received the radioprotective agents throughout their lifetime, another group did not (unprotected group). In rats that received a single dose of radiation, the overall tumor induction rate was 49.4% in protected animals and 50.8% in unprotected animals; the latency time was 240-542 days. The tumors included osteogenic osteosarcomas in 44%, chondrosarcoma in 1.8%, and adenoma of the adrenal cortex in 1.8%. In the group treated daily with the radioactive mixture, the overall tumor induction rate was 12.7% vs 12.6% in the unprotected group. The latency time was 309-667 days. There were no bone tumors in the protected group and only four malignant tumors (7.3%, all lymphoreticular sarcomas) were found, but the incidences of osteogenic osteosarcoma and lymphoreticular sarcoma were 3.6% and 9.0%, respectively, in the unprotected group. Dosimetric measurements revealed that the radioprotective agents reduced the whole-body absorption of ^{137}Cs by 17 times and the skeletal absorption of ^{90}Sr by nearly 4 times. The findings indicate that there is a protective action of Prussian Blue, sodium alginate, and calcium phosphate during long-term irradiation. (13 refs.)

7-6300 **Long-Term Effects of Radium Exposure in Female Dial Workers. Hematocrit and Blood Pressure.** (Eng) Polednak, A. P. (Center Human Radiobiology, Radiological Environmental Res. Div., Argonne Natl. Lab., Argonne, IL 60439). *Environ Res* 13(2): 237-249; 1977.

Hematocrit levels and systolic and diastolic blood pressure were measured in two groups of female radium dial workers employed before or after 1930. Internal comparisons of these variables were made by dose groups, using an av skeletal dose estimated several years following exposure to 228 Ra and 226 Ra; external comparisons were made using data from the US National Health Survey. Analysis of dial workers employed before 1930 suggests that there is a small but statistically

significant long-term effect of high-dose radium exposure on mean hematocrit levels in older persons. For the 65- to 74-yr-old workers, the mean hematocrit level was 41.3 in the > 100-rad dose group, and 43.0 in the 0- to 9-rad and 10- to 99-rad groups, a statistically significant decrease. Furthermore, in the workers aged 65-74 yr, the mean hematocrit was lower in persons with malignant tumors (40.0) than in persons with benign tumors (42.1) or no tumors (41.2). According to published standards, however, using internal and external control groups, the high-dose group (> 100 rads) did not have a higher frequency of low hematocrit readings suggestive of anemia. There were no differences in mean hematocrit levels among the three dose groups at 55-64 yr of age. It could not be determined from the data if the apparent dose effect in the older groups represents a residual effect or a decline with age. There was no relationship between dose and blood pressure in women exposed before 1930. In women exposed from 1930 to 1954, dose was a significant predictor of systolic blood pressure in those 45-54 yr old, but not in those 55-64 yr old. It was concluded that long-term effects of radium exposure do not include a clinically significant lowering of hematocrit. (35 refs.)

77-6301 **Planimetric Evaluation and Comparison of Roentgenograms of Osteogenic Sarcomas Induced by ^{226}Ra and ^{224}Ra in Mice.** (Eng.) Svoboda, V. (Inst. Hygiene and Epidemiology, Center Radiation Hygiene, 100 42 Prague, Czechoslovakia); Kofranek, V.; Kotaskova, Z.; Bubenikova, D.; Dvorak, V. *Neoplasma* 24(3): 311-318; 1977.

Differences in the localization, size, growth kinetics, and morphological features of ^{224}Ra - and ^{226}Ra -induced osteosarcomas in mice were determined. Three activity levels of ^{226}Ra were injected ip to 500 female ICR mice at the age of 10 wk: 8.8, 24.6 and 70.5 $\mu\text{Ci/kg}$. Three levels of ^{224}Ra were also administered ip (300 mice), but in fractionated doses at 3- and 4-day intervals over a period of 75 wk. The total activity per mouse was 0.65, 1.88, 5.22 μCi . Seventy-four tumors were induced by ^{226}Ra and 89 by ^{224}Ra . The tumors were evaluated by planimetric measurements of the roentgenograms that were made. Those induced by ^{224}Ra were diagnosed earlier. The distribution of the ^{224}Ra and ^{226}Ra series was, respectively, long bones, 32 and 13 tumors; vertebrae, 30 and 24; other skeletal areas, 27 and 37. The ^{224}Ra tumors were, on the av, larger and the degree of calcification was not as extensive as that in the ^{226}Ra tumors. The survival time of the tumor-bearing mice was 463 days for the ^{224}Ra group and 501 days for the

^{226}Ra group. It is probable that the incidence and some of the features of the osteosarcomas depend on the time and tissue distribution of the dose delivered. (13 refs.)

- 77-6302 **Mean Bone Marrow Dose of Atomic Bomb Survivors in Hiroshima and Nagasaki.** (Eng.) Hashizume, T. (Natl. Inst. Radiological Sciences, 9-1, 4-chome, Anagawa Chiba 280, Japan); Maruyama, T.; Nishizawa, K.; Fukuhisa, K. *J Radiat Res* 18(1): 67-83; 1977.

Using a Snyder mathematical phantom, ratios of the mean bone marrow-absorbed dose of radiation to the in-air tissue-absorbed dose were determined for survivors of atomic bomb radiation. Ratios were corrected for the angular distribution of incident radiation, and mean bone marrow doses were estimated as a function of distance from the hypocenter (Hiroshima, 1,022 m; Nagasaki, 866 m), assuming survivors were standing in an open field during exposure. Resultant ratios are tabulated in rads as a function of the incident angles on survivors for initial γ -rays and neutrons (including recoil protons and $\text{H}(n,\gamma)^2\text{D}$ and $^{14}\text{N}(n,p)^{14}\text{C}$ reactions). Dose ratios are at a max when survivors were exposed with the geometry of posterior radiation. Of importance for the estimation of radiation leukemogenesis among survivors is the fact that dose ratios for children were significantly larger than those for adults. In Hiroshima, the contribution of protons, a major cause of elevated RBE (relative biological effectiveness) values of neutron radiation, was about 25%, whereas in Nagasaki it was about 4%. (15 refs.)

- 77-6303 **DNA Repair in V-79 Cells Treated with Combinations of Ultraviolet Radiation and N-Acetoxy-2-acetylaminofluorene.** (Eng.) Ahmed, F. E. (Biology Dept., Brookhaven Natl. Lab., Upton, NY 11973); Setlow, R. B. *Cancer Res* 37(9): 3414-3419; 1977.

DNA repair in V-79 Chinese hamster cells was investigated following combined treatment with UV radiation and N-acetoxy-2-acetylaminofluorene (AAAF), and the results were compared with those previously obtained in human fibroblasts. Unscheduled synthesis was almost saturated at a UV dose of 20 Joules/meter² and an AAAF concentration of 20 μM . After a combined treatment, however, DNA synthesis was less than additive at saturation; at high doses, the amount of unscheduled DNA synthesis was less than that from UV or AAAF alone. Thus AAAF treatment inhibited unscheduled synthesis resulting from UV treatment and vice versa. Similar results were found when AAAF was added immediately after UV and with AAAF pretreatment for 20 min. Bromodeoxyuridine photolysis revealed that repair from combined treatment was less than from individual treat-

ments. *Micrococcus luteus* endonuclease allowed the measurement of reduced UV repair in the presence of AAAF, while no AAAF repair was measurable with this technique. It was concluded that V-79 cells are different from human fibroblasts in the excision repair of UV and AAAF damage and that both kinds of damage inhibit repair of damage due to the other agent. (27 refs.)

- 77-6304 **DNA Replication Kinetics in X-irradiated Chinese Hamster Ovary Cells.** (Eng.) Gerner, E. W. (Univ. Arizona Coll. Medicine, Dept. Radiology, Div. Radiation Oncology, Tucson, AZ 85724). *Radiat Res* 71(2): 387-397; 1977.

DNA replication kinetics were studied in x-irradiated Chinese hamster ovary (CHO) cells. Synchronous and asynchronous CHO cultures were exposed to total x-ray doses ranging from 150 to 3,000 rads. X-irradiation caused a temporary inhibition of cell division such that a 500-rad dose resulted in a division delay of approx 5 hr. Cultures irradiated with 3,000 rads 3 hr after mitosis (ie early-mid G_1) were blocked in G_1 for approx 0.5 hr, but eventually they replicated the same amount of DNA at the same rate as control cultures. When cells were irradiated 5.5 hr after mitosis (near the G_1/S boundary), 500 rads were completely without effect on DNA replication kinetics; 3,000 rads inhibited DNA replication for a time, but these cells eventually replicated near-normal amounts of DNA at approx normal rates. A dose of 500 rads in the mid-S phase (9 hr after mitosis) had no effect on DNA replication kinetics, but 1,000 rads caused a slight depression. Cultures in mid-S irradiated with 3,000 rads showed a marked depression in DNA replication rate. Irradiation of asynchronous cultures with 150-3,000 rads reduced DNA replication at all doses. This effect appeared to be dose-independent in the range 150-1,000 rads for up to 5 hr after irradiation, after which it was dose-dependent over the complete dose range. (21 refs.)

- 77-6305 **Split-Dose Recovery for Radiation-Induced Tumors in Rat Skin.** (Eng.) Burns, F. J. (Inst. Environmental Medicine, New York Univ. Medical Center, 550 First Ave., New York, NY 10016); Vanderlaan, M. *Int J Radiat Biol* 32(2): 135-144; 1977.

Tumor-related recovery in the skin of male CD rats was estimated from the dependence of tumor yield on time between split doses of electron radiation. At 1,000, 1,450, and 2,300 rads, the exposures were split into two equal doses spaced at intervals of 1, 3, and 6.3 hr. At the end of either 64 or 70 wk, the skin and tumors were examined histologically. Results show that the effect of split doses on tumor yield depended on the position on the dose-response curve. At the

lowest split dose, the yield declined with a half-time of about 1.8 hr; at the intermediate split-dose, an initial increase was followed by a decline with a half-time of about 3.9 hr; at the highest split dose, the tumor yield increased with time between exposures. Fractionation-induced increases in tumor yield were explained as a sparing effect on cell lethality, whereas tumor-related recovery per se was indicated at the lower two doses. (11 refs.)

77-6306 **Light-induced Mutagenicity of Neutral Red (3-Amino-7-dimethylamino-2-methylphenazine Hydrochloride).** (Eng.) Gutter, B. (Dept. Microbiology, New York Medical Coll., Valhalla, NY 10595); Speck, V. T.; Rosenkranz, H. S. *Cancer Res* 37(4): 1112-1114; 1977.

Illumination of *Salmonella typhimurium* with visible light in the absence of added photosensitizers resulted in an increased

number of mutations in strain TA1535 (specific for base substitutions). Illumination in the presence of neutral red led to a further increase in light-induced mutants. (26 refs.)

See also:

*(Rev.): 77-6005, 77-6020, 77-6073, 77-6074, 77-6075, 77-6077, 77-6078, 77-6079, 77-6080, 77-6081, 77-6082, 77-6083, 77-6084, 77-6104, 77-6116, 77-6125.

*(Chem.): 77-6170, 77-6280, 77-6293.

*(Viral): 77-6342, 77-6346.

*(Immun.): 77-6465.

*(Path.): 77-6497, 77-6518, 77-6521.

*(Epid.-Biom.): 77-6577, 77-6578, 77-6579, 77-6580.

VIRAL CARCINOGENESIS

- 77-6307 **Induction of Two Transformation-sensitive Membrane Polypeptides in Normal Fibroblasts by a Block in Glycoprotein Synthesis or Glucose Deprivation.** (Eng) Pouyssegur, J. (Centre de Biochimie, Université de Nice, Parc Valrose-06034, Nice, France); Shiu, R. P.; Pastan, I. *Cell* 11(4): 941-947; 1977.

Chick embryo fibroblasts (CEF) that were transformed by avian RNA tumor viruses contained increased amounts of two membrane polypeptides (75,000 and 90,000 daltons). These polypeptides were also increased in AD6, a 3T3 fibroblast mutant defective in glycoprotein synthesis. When AD6 were fed N-acetylglucosamine, a metabolite that bypasses the metabolic block, the 75,000-dalton protein was markedly reduced, the 90,000-dalton peptide disappeared, and a fully glycosylated 92,000-dalton derivative appeared. Adding glycosylation inhibitors such as glucosamine and 2-deoxyglucose to normal CEF and 3T3 cells induced accumulation of the 75,000- and 90,000 dalton polypeptides. Glucose deprivation for 24-48 hr also induced these two proteins in normal fibroblasts. These results suggest that the 75,000- and 90,000 dalton membrane proteins are not directly related to transformation, but are more likely to be involved in glucose utilization by normal fibroblasts. (29 refs.)

- 77-6308 **Expression of Viral Protein P27 in Avian Sarcoma Virus-transformed Mammalian Cells and Helper-dependent Rescue of Rous Sarcoma Virus.** (Eng.) Popovic, M. (Cancer Res. Inst., Slovak Acad. Sciences, Bratislava, Czechoslovakia); Svoboda, J.; Suni, J.; Vaheri, A.; Ponten, J. *Int J Cancer* 19(6): 834-842; 1977.

Avian sarcoma virus (ASV)-transformed mammalian cells were tested for viral gene products: p27, the viral structural polypeptide, by radioimmunoassay and group-specific (gs) antigens by complement fixation. Clones of B77 virus-producing RBE rat tumor cells had p27 concentrations of 10-80 nanograms/mg cellular protein; the poorest virus-producing clone had the lowest levels of p27 and gs antigen. Treatment of the clones with halogenated pyrimidines, 5-bromodeoxyuridine (BUdR), and 5-iododeoxyuridine (IUdR) had little effect. Virogenic rat cell lines XC and LWC3 and human 118MG/EH cells transformed by the Prague, Schmidt-Ruppin, and Engelbreth-Holm strains of ASV, respectively, were analyzed after fusion of the X-irradiated cells with chicken fibroblasts. Concentrations of p27 and gs antigens and tumor induction by intact cells were the same in the XC cells and the 118MG/EH cells. Treatment with BUdR or IUdR increased the p27 level in 119MG/EH. Rat LWV3 cells had no detectable p27 or gs antigens, but their

tumor-inducing activity in chickens was 50 times higher than that of the XC and 118MG/EH cells. Nonvirogenic rat TWERC cells, transformed by Prague RSV, had low detectable levels of p27 and gs antigens but did not produce tumors in chickens or foci when fused with chicken fibroblasts. The RSV genome was successfully rescued from TWERC cells by the fusion of these cells with Rous-associated virus 1-preinfected chicken fibroblasts. The rescued virus had a one-hit titration pattern in duck embryo fibroblasts, indicating that the virus was nondefective for infection and transformation of these cells. (40 refs.)

- 77-6309 **Variations in Integration Site of Avian Oncornavirus in Different Hosts.** (Eng) Dastoor, M. N. (Dept. Microbiology and Immunology, Univ. California Sch. Medicine, Los Angeles, CA 90024); Shoyab, M.; Baluda, M. A. *J Virol* 21(2): 541-547; 1977.

The integration site of B-77 avian sarcoma virus and a Rous associated virus (RAV-61) was investigated in permissive duck embryo fibroblasts and nonpermissive mouse 3T3 cells. These systems represent different host responses to viral infection: (1) both cellular transformation and viral replication occur in B-77-infected duck cells, (2) only viral replication occurs in RAV-61-infected duck cells, and (3) only transformation occurs in B-77-infected 3T3 cells. The DNA's from RAV-61- or B-77-infected duck cells or from B-77 infected mouse cells had an av fragment size of 2.8 to 3.0 x 10⁶ daltons in single-stranded form. Both B-77 and RAV-61 integrated in the unique region of duck DNA; B-77 proviral DNA was associated with both repeated and unique host DNA sequences in transformed 3T3 cells. These findings suggest that if cellular reiterated DNA sequences are involved in transcription regulation, they need not be adjacent to the structural genes they control. However, oncornaviruses may contain information that regulates their own transcription. (25 refs.)

- 77-6310 **Changes in Phosphatidylinositol Metabolism Correlated to Growth State of Normal and Rous Sarcoma Virus-Transformed Japanese Quail Cells.** (Eng.) Diringer, H. (Robert Koch-Institut, Nordufer 20, 1000 Berlin-65, W. Germany); Friis, R. R. *Cancer Res* 37(9): 2979-2984; 1977.

The metabolism of phospholipids in normal and Rous sarcoma virus-transformed Japanese quail cells was studied. There were no differences in lipid compositions between normal and tumor cells or between cells under different culture conditions. The metabolism of phosphatidylserine and sphin-

omyelin was unaffected. That of the choline and ethanolamine glycerophospholipids, however, differed according to culture conditions for both cell types. The only difference in phospholipid metabolism between normal and tumor cells was a lack of response in the kinetics of release of ^{32}P -phosphate from phosphatidylinositol (PI) in tumor cells under conditions of high population density or serum depletion. Hence, release of ^{32}P -phosphate from PI is the only parameter of phospholipid metabolism that correlates with growth. (34 refs.)

7-6311 **Incomplete Viral Genome in a Non-virogenic Mouse Tumour Cell Line (RVP₃) Transformed by Prague Strain of Avian Sarcoma Virus.** (Eng.) Svoboda, (Inst. Molecular Genetics, Czechoslovak Acad. Sciences, Prague 6, Czechoslovakia); Popovic, M.; Sainerova, H.; Mach, O.; Shoyab, M.; Baluda, M. A. *Int J Cancer* 19(6): 851-858; 1977.

Two cell lines, RVP₃ and RVA₄, originally derived from mouse tumors induced by the Prague and Schmidt-Ruppin (SR) strains of Rous sarcoma virus (RSV), respectively, were studied. Cell-fusion experiments showed that RVP₃ cells could not be induced to produce RSV by fusion with chicken indicator cells, even when the latter were producing avian leukosis viruses. When the transfection assay was used, there was no RSV production or morphological transformation of cultures treated with DNA from RVP₃ cells even after 40 days of observation. Molecular hybridization indicated that RVP₃ cells harbored 31%-45% of the viral genome sequences. The tumor cell line RVA₄ did not contain any detectable viral sequences. The RVP₃ cells are designated cryptovirogenic, ie, cells harboring only part of the provirus, which is not inducible and cannot be complemented by indicator cells even if the latter produce helper viruses. If truly cryptovirogenic-transformed mammalian cells could be identified, they would represent a useful model for the study of "sarc" and related gene sequences of transforming avian sarcoma viruses and their products. The absence of SR-RSV proviral sequences in RVA₄ tumor cells raises questions concerning the etiological role of SR-RSV. (26 refs.)

7-6312 **Identification of a Transformation-specific Antigen Induced by an Avian Sarcoma Virus.** (Eng.) Brugge, J. S. (Dept. Pathology, Univ. Colorado Medical Center, Denver, CO 80262); Erikson, R. L. *Nature* 269(5626): 346-348; 1977.

Serum from rabbits with Schmidt-Ruppin (SR) strain avian sarcoma virus (SR-ASV)-induced tumors that follow two different growth patterns has allowed the detection of a 60,000-dalton protein that has the properties of ASV transformation-specific antigen. This protein was found in SR-ASV-transformed chicken cells and SR-ASV-induced hamster tu-

mor cells, but not in other SR-ASV-transformed cells or in other D-type virus-transformed cells. The polypeptide loses its antigenicity at 41 C and is thought to be a product of the *src* gene. Further studies on the characterization of this gene and its product may indicate the mechanism of ASV-induced oncogenesis. (14 refs.)

77-6313 **Levels of Translatable mRNAs for Cell Surface Protein, Collagen Precursors, and Two Membrane Proteins Are Altered in Rous Sarcoma Virus-transformed Chick Embryo Fibroblasts.** (Eng.) Adams, S. L. (Lab. Molecular Biology, NCI, NIH, Bethesda, MD 20014); Sobel, M. E.; Howard, B. H.; Olden, K.; Yamada, K. M.; de Crombrughe, B.; Pastan, I. *Proc Natl Acad Sci USA* 74(8): 3399-3403; 1977.

The relative amounts of functional messenger RNA's (mRNA's) for several transformation-sensitive proteins were measured to determine the mechanism responsible for the decreased production of these proteins. Total cellular RNA's extracted from normal chick embryo fibroblasts (CEF) and from CEF transformed by Schmidt-Ruppin Rous sarcoma virus (RSV) were translated in a cell-free system derived from wheat germ. The translation products were analyzed by immunoprecipitation, collagenase digestion, and sodium dodecyl sulfate/polyacrylamide gel electrophoresis. This analysis showed a fivefold reduction in translatable mRNA for two collagen precursors in the CEF transformed by RSV. Increases in functional mRNA's were observed for myosin and for two membrane polypeptides with mol wts of 95,000 and 78,000; the latter two proteins increased upon transformation, but these increases were secondary to the rapid depletion of glucose from the medium that occurs with transformed cells. These results show that the decrease in cell surface protein and in collagen upon transformation of CEF by RSV is reflected by a decrease in functional mRNA for these proteins. This suggests that some of the major cellular changes induced by oncogenic viruses could be due to changes in the activity of specific cellular genes. (34 refs.)

77-6314 **In Vitro Translation Yields a Possible Rous Sarcoma Virus *src* Gene Product.** (Eng.) Bee-mon, K. (Tumor Virology Lab., Salk Inst., San Diego, CA 92112); Hunter, T. *Proc Natl Acad Sci USA* 74(8): 3302-3306; 1977.

The translation of virion RNA's from Rous sarcoma virus (RSV) and a transformation-defective (td) deletion mutant of RSV was investigated in the messenger-dependent reticulocyte lysate system. The translation products were analyzed by sodium dodecyl sulfate-polyacrylamide slab gel electrophoresis and fluorography. The major product of both RSV and tdRSV was a 76,000-dalton (da) protein. There were two doublets, at 25,000 and 17,000 da, in the translation products

of RSV RNA that were absent from those of td RSV RNA. Synthesis of the 25,000- and 17,000-da proteins was not sensitive to inhibition by m⁷GTP, but synthesis of the 76,000-da protein was. Tryptic peptide maps showed that the 25,000- and 17,000-da proteins are related to one another but are distinct from the 76,000-da protein. The 25,000-da protein was translated only from a polyadenylated RNA of 2,500 nucleotides, whereas the 76,000-da protein was translated from 38S RNA, which corresponds to the entire viral genome. Both viral RNA's also coded for the synthesis of a small amount of a 180,000-da protein that has tryptic peptides in common with the 76,000-da protein. From the absence of the 25,000- and 17,000-da proteins in the translation products of td RSV RNA and the size of their RNA templates, it is concluded that these proteins may be derived from coding sequences within the RSV *src* gene. From the similarity of the messenger RNA sizes for the 180,000- and 76,000-da proteins, the relatedness of their tryptic peptides, and the common sensitivity of their synthesis to m⁷GTP, it is concluded that the synthesis of both is initiated at the initiation site for the *gag* gene. (21 refs.)

- 77-6315 Type C Viral *gag* Gene Expression in Chicken Embryo Fibroblasts and Avian Sarcoma Virus-transformed Mammalian Cells.** (Eng.) Reynolds, F. H. (Viral Oncology Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701); Hanson, C. A.; Aaronson, S. A.; Stephenson, J. R. *J Virol* 23(1): 74-79; 1977.

Competition radioimmunoassays were used to determine the presence of avian C-type *gag* gene precursor polypeptides and their intermediate cleavage products in avian embryo cells and mammalian cells transformed by avian sarcoma viruses, in an attempt to order genetic sequences coding for individual viral proteins within the avian C-type viral *gag* gene. Rous-associated virus (RAV-0)-positive chicken embryo cells expressed proteins p27, p19, p15, and p12. Virus-negative chicken embryos expressed relatively high levels of p27, p19, and p12 but only a low level of p15. A 60,000-dalton component with antigenic determinants for p27, p19, and p12 was found in extracts from these virus-negative chick embryos, suggesting a terminal position for p15 within the *gag* gene. A 35,000- to 40,000-dalton component with p12 and p27 antigenic determinants was also detected, indicating that p12 and p27 may occupy adjacent positions. The tentative assignment for the avian C-type viral *gag* gene-coded precursor sequence was NH₂-p19-p12-p27-p15-COOH. Implications of these findings regarding the restriction to endogenous avian leukemia expression in both virus antigen-positive chicken embryo cells and avian sarcoma virus-transformed mammalian cells are discussed. (32 refs.)

- 77-6316 Genetic Variation in the RNA Transcripts of Endogenous Virus Genes in Uninfected Chicken**

Cells. (Eng) Wang, S. Y. (Rockefeller Univ., New York, NY 10021); Hayward, W. S.; Hanafusa, H. *J Virol* 24(1): 64-73; 1977.

The size distribution and genetic content of virus-specific RNA were studied in uninfected chick embryos of two different phenotypes: (1) cells positive for both group-specific (gs) antigens and chicken helper factor (*chf*), and (2) noncoordinate cells with low gs-antigen levels but high helper activity. Two major size classes of polyadenylic acid-containing RNA homologous to the avian leukosis virus genome, were detectable in cells of both types. The larger RNA, which contained most of the sequences of the leukosis virus genome, was 31S in gs+chf+ cells but 35S in the noncoordinate cells. Analysis of the viral RNA with gene-specific complementary DNA probes indicated that the 31S RNA lacked portions of the *gag* and *pol* genes. A smaller RNA species, which sedimented at 21S in both cell types, was a transcript of the 3'-proximal portion of the viral genome, consisting of the *env* gene and the common sequences. The amount of *env*-specific RNA in the 21S region was more than six times higher in the noncoordinate cells than in the gs+chf+ cells; this difference was concordant with the five- to tenfold higher *chf* activity in the noncoordinate cells. The endogenous viral RNA in uninfected cells and the RNA from Rous-associated virus-O virion hybridized only partially with DNA complementary to the common region of the Rous-associated virus genome, but the RNA of all exogenous viruses tested hybridized almost completely to this complementary DNA. Small amounts of *src*-specific polyadenylated RNA were also present in uninfected chicken cells. This RNA sedimented as a single peak at 26S and was not covalently linked to any other identifiable virus-specific RNA sequences. The amount of *src* RNA was the same in both cell types and also in gs-chf- cells, indicating that transcription of cellular sequences homologous to the *src* gene is independent of transcription of other endogenous viral genes. (46 refs.)

- 77-6317 Adenylate Cyclase Activity and the cAMP Level Are Not Directly Correlated with Transformation by Avian Sarcoma Viruses.** (Eng) Yoshida, M. (Lab. Viral Oncology, Cancer Inst., Toshima-ku, Tokyo, Japan); Ikawa, Y.; Owada, M.; Toyoshima, K. *Int J Cancer* 20(4): 560-563; 1977.

Adenylate cyclase activity was measured in chick embryo fibroblasts (CEF) infected with temperature-sensitive mutants (ts) of avian sarcoma virus (ASV). When CEF transformed with a ts mutant at 36 C were incubated at the nonpermissive temperature (41 C), recovery from the low adenylate cyclase activity detectable in the transformed state was slower than the disappearance of signs of morphological transformation. After a downward temperature shift, the activity decreased, and this change was also slower than the alteration of cell morphology. The affinity of the enzyme sys-

for ATP also changed after, and not during, morphological alteration. No significant difference was observed between cyclic AMP levels in ASV-transformed and noninfected CEF. These findings are consistent with the idea that adenylate cyclase is not involved in cell transformation and that the change in its activity is secondary to cell transformation. (7 refs.)

77-6318 Measurement of Proviral Genes in Uninfected and Avian Myeloblastosis Virus-infected Cells by Hybridization with ³H-labeled Complementary DNA Probe Excess. (Eng) Heilmann, L. J. (Dept. Agricultural Chemistry, Oregon State Univ., Corvallis, OR 97331); Herlihy, T. M.; Beaudreau, G. S. *J Virol* 24(2): 498-504; 1977.

Hybridization kinetics were examined in avian myeloblastosis virus (AMV)-infected cells using an excess of ³H-labeled complementary DNA (cDNA) as a probe. The DNA was removed from RBC nuclei of normal chickens and from RBC and myeloblast nuclei of AMV-infected chickens. When excess ³H-cDNA was used to drive the reaction with viral RNA (vRNA), the same rate constant was obtained as when an excess of vRNA was used as the driver-33.2 cpm/mole · sec. The specific activities for the probe, estimated from kinetic measurements of the hybridization reaction and from the amount of ³H-cDNA in hybrid form at equilibrium, were 9.1 and 8.6 cpm/micogram, respectively. Probe excess hybridization analysis of the amount of vDNA sequences in the infected nuclei revealed that uninfected RBC had 5-6 viral genome equivalents per cell but RBC from AMV-infected chickens had 10-12 genome equivalents per cell, corresponding to an addition of 5-6 genome equivalents with infection. DNA from infected myeloblasts revealed that about 15 genome equivalents were added with AMV infection. The advantages of this procedure over other hybridization procedures are discussed. (8 refs.)

77-6319 Frog Oocytes Synthesize and Completely Process the Precursor Polypeptide to Virion Structural Proteins after Microinjection of Avian Myeloblastosis Virus RNA. (Eng.) Ghysdael, J. (Faculte Agronomique de l'Etat, 5800-Gembloux, Belgium); Hubert, E.; Travnick, M.; Polognesi, D. P.; Burny, A.; Cleuter, Y.; Huez, G.; Kettmann, R.; Marbaix, G.; Portetelle, D.; Chantrenne, H. *Proc Natl Acad Sci USA* 74(8): 3230-3234; 1977.

The messenger capacity of avian myeloblastosis virus (AMV) RNA was tested in the cellular protein-synthesizing system of *Xenopus laevis* (frog) oocytes. Oocytes were microinjected with a 60S-70S RNA aggregate or its 30S-40S subunits and incubated for 48 hr in culture medium containing ³⁵S methionine. Chick embryo fibroblasts (CEF, both uninfected or infected with AMV) pulse-labeled with ³⁵S methionine for 5 min

or pulse-labeled for 5 min and chased for 60 min were used as standards for AMV-specific protein synthesis. Immunoprecipitates from microinjected and control oocytes, together with those of infected and noninfected CEF, were submitted to electrophoresis on the same sodium dodecyl sulfate/polyacrylamide slab gel. The results indicated that injection of AMV RNA into oocytes directed the synthesis of at least 10 virus-specific polypeptides. The patterns were qualitatively and quantitatively similar regardless of whether the 60S-70S AMV RNA aggregate or its 30S-40S subunits were used. Three of these polypeptides, with mol wts of 28,000, 21,500, and 17,500 daltons, comigrated with virion structural proteins p27, p19, and p15/p12. Pulse-chase experiments indicated that the 76,000-mol wt polypeptide (Pr76) was gradually cleaved into smaller intermediate precursors and then into authentic virion proteins. The processing pattern was the same in the oocytes as in CEF infected with AMV, but the processing took place at a much slower rate. These results suggest that the posttranslational cleavage machinery present in AMV-infected CEF also exists in injected oocytes. (26 refs.)

77-6320 Synthesis by Avian-Myeloblastosis-Virus RNA-dependent DNA Polymerase of Discrete Reverse Transcripts of Bacteriophage RNA Polyadenylated In Vitro. (Eng) Devos, R. (Laboratorium voor Moleculaire Biologie, Faculteit der Wetenschappen, Rijksuniversiteit te Ghent, K. Lod Ledeganckstraat 35, B-9000 Ghent, Belgium); Van Emmelo, J.; Celen, P.; Gillis, E.; Fiers, W. *Int J Biochem* 79(2): 419-432; 1977.

In the presence of oligo(dT) as a primer, several polyadenylated viral RNA's were excellent templates for the synthesis of complementary DNA (cDNA) using RNA-dependent DNA polymerase from avian myeloblastosis virus. If deoxythymidine triphosphate (dTTP) was the only deoxynucleoside triphosphate present, the reverse transcriptase catalyzed a "slippage" reaction on the poly(A) tail, especially at dTTP concentrations > 1 μM. In the case of bacteriophage MS2 RNA-poly(A), this poly(dT) synthesis could be specifically inhibited, but not completely abolished, by addition of deoxyguanosine triphosphate. Lowering the dTTP concentration also decreased the av size of the poly(dT) products. In the presence of all four deoxynucleoside triphosphates (dNTP's), discrete partial transcripts could be synthesized that were complementary to the 3'-terminal region of viral RNA. Although the av size of the products increased at higher incubation temperatures, the pattern of the labeled transcripts, as revealed by gel electrophoresis, depended mainly on the nature of the dNTP in limiting concentration. These results indicate that the primary sequence of the template is the major determinant of the discrete partial transcripts. Restricted synthesis, using three or less dNTP's, resulted in small cDNA products. The successive incorporation of the different dNTP's added to the primer, using MS2 RNA-poly(A) or Q β RNA-poly(A) as a template, was in complete agreement

with the known 3'-terminal sequence. Under the conditions used and with MS2 RNA-poly(A) or poly(A) as template, a ribosyl primer could not be substituted for the deoxyribosyl primer. Similarly, with MS2 RNA-oligo(C), only (dG)₁₀ was an efficient primer for reverse transcription. Ribonucleoside triphosphates were poor substrates. (21 refs.)

- 77-6321 In Vitro Transcription of the Avian Retrovirus Genome by the α Form of the Viral RNA-directed DNA Polymerase.** (Eng) Collett, M. S. (Dept. Microbiology, Univ. Minnesota Medical Sch., Minneapolis, MN 55455); Grandgenett, D. P.; Faras, A. J. *J Virol* 24(2): 704-708; 1977.

The in vitro transcription of the avian retrovirus genome by the α form of viral RNA-directed DNA polymerase was examined and compared to transcription by the $\alpha\beta$ form of the molecule. Divalent cation requirements using native 70S RNA, 35S viral subunit RNA to which purified tRNA^{trp} primer had been reannealed, and 35S RNA to which oligo(dT)₁₂₀₁₈ had been added as template-primer complexes revealed that the α form had a preference for Mn²⁺, but the $\alpha\beta$ form preferred Mg²⁺. Transcription patterns of both forms of the enzyme were identical when these three template-primer complexes were used. The characteristics of α DNA polymerase transcription at high concentrations of deoxynucleotide triphosphates were identical to those of the $\alpha\beta$ form. Analysis of the secondary structure of DNA products from the α form revealed that it is deficient only in the synthesis of true duplex DNA; it maintains its ability to form hairpin DNA initiated from the tRNA^{trp} primer at the 5' end of the viral genome. This may be a function of the location of the major transcription site on the viral genome and/or the nature of the primer for synthesis of the second DNA strand. (39 refs.)

- 77-6322 Avian Myeloblastosis Virus RNA Is Terminally Redundant: Implications for the Mechanism of Retrovirus Replication.** (Eng) Stoll, E. (Institut für Molekularbiologie I, Universität Zürich, 8093 Zürich, Switzerland); Billeter, M. A.; Palmenberg, A.; Weissmann, C. *Cell* 12(1): 52-72; 1977.

The terminal heteropolymeric sequences of avian myeloblastosis virus (AMV) RNA were determined by the following procedures: (1) RNA sequence determination on the 5' terminal and the poly(A)-linked 3' terminal T1 oligonucleotides and (2) analysis by a method of AMV 'strong-stop' DNA and of DNA complementary to the poly(A)-linked T1 oligonucleotide, synthesized with reverse transcriptase and (pdT)₁₃ as primer. The structure deduced for the 5' terminal region is (5')7m GpppGmCCAUUCUACCUCACACCAUUG-GUGUGCACCUGGGUUGAUGGCCGGACCGUCGAU-UCCCUGACGACUACGAGCACCUGCAUGAAGCA-

GAAGGCUUCAU. Two distinct 3' terminal sequences were deduced: GCCAUUCUACCUCUCAAAA ... A-OH and GCCAUUCUACCUCUACCAAAA ... A-OH. The two termini, differing by a C-C-A sequence, may reflect genetic heterogeneity of the AMV stock, or they may be generated at or after RNA transcription. These results demonstrate a terminal redundancy of the heteropolymeric sequence of 16 and 19 nucleotides, respectively. The terminal redundancy makes possible the transfer of the DNA segment synthesized on the 5' terminal redundant sequence. (61 refs.)

- 77-6323 Interaction of Tryptophan tRNA and Avian Myeloblastosis Virus Reverse Transcriptase: Further Characterization of the Binding Reaction.** (Eng) Haseltine, W. A. (Sidney Farber Cancer Center, Harvard Medical Sch., Boston, MA 02115); Panet, A.; Smoler, D.; Baltimore, D.; Peters, G.; Harada, F.; Dahlberg, J. E. *Biochemistry* 16(16): 3625-3632; 1977.

The interaction between the primer cellular tryptophan-transfer RNA (tRNA-Trp) and avian myeloblastosis virus (AMV) reverse transcriptase was investigated. Anti-reverse transcriptase IgG inhibited both DNA polymerase activity and tRNA-Trp binding; N-ethylmaleimide inhibited only the ability of the enzyme to bind to tRNA; nonspecific rat IgG inhibited neither of the bindings. tRNA-Trp was 10 to 15 times more efficient for binding than unfractionated chick cell tRNA, suggesting that most tRNA species are unable to compete for tRNA-Trp binding. Binding studies indicated that none of the 3' or 5' fragments of modified tRNA-Trp bound to the enzyme, suggesting that a three-dimensional structure is necessary for binding. In other binding studies, AMV reverse transcriptase bound to tRNA that had been charged with tryptophan or methionine, but not to tRNA charged with lysine or phenylalanine. In addition, the α subunit of the enzyme does not bind tightly to tRNA-Trp or to tRNA-Pro, the primer for initiation of the reverse transcriptase of Moloney murine leukemia virus. (32 refs.)

- 77-6324 Immunological Approach to Studies of the Role of Reverse Transcriptase of Oncornaviruses in Neoplastic Processes.** (Rus.) Graevskaia, N. A. (Inst. Poliomyelitis and Viral Encephalitis, Acad. Medical Sciences USSR, Moscow, USSR); Sito, A. F. *Vestn Akad Med Nauk SSSR* (5): 55-59; 1977.

Immune sera from rabbits immunized with purified reverse transcriptase (RT) from avian myeloblastosis virus (AMV) showed specific inhibition of RT activity. The absence of cross-reactivity between AMV RT and antibodies to the structural viral proteins indicates immunological differences between RT and proteins of the AMV capsule, group-specific antigen, and nucleotide. (22 refs.)

- 77-6325 **Interaction of Oncornaviral Proteins Separated by SDS-PAGE with Antibodies in Immunodiffusion.** (Eng.) Polakova, K. (Cancer Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia); Russ, G. *Neoplasma* 24(3): 245-248; 1977.

The use of gel slices obtained directly after sodium dodecyl sulfate-polyacrylamide gel (SDS-PAGE) electrophoresis as a source of defined oncornaviral polypeptides in gel double immunodiffusion (ID) was examined. SDS-PAGE slices, buffered 1% agarose (pH 7.0), and rabbit or hamster antisera were effective in analyzing labeled BAI-A strain avian myeloblastosis virus (AMV) polypeptides. Immunoprecipitation lines corresponding to AMV polypeptides p27 and p19 were most evident and usually appeared within 24 hr. Precipitin lines for p15 and p12 were less distinct. This procedure may prove useful for the rapid analysis of individual viral polypeptides and for testing relationships between subunits, multimers, peptide fragments, and cross-linked complexes from other oncornaviruses. (15 refs.)

- 77-6326 **Interaction of Sindbis Virus with Oncornavirus-producing Cell Cultures.** (Rus.) Gushchin, B. V. (D. I. Ivanovsky Inst. Virology, Moscow, USSR); Berezina, L. K.; Guschchina, E. A.; Lvov, D. K.; Klimenko, S. M.; Zhdanov, V. M. *Vopr Virusol* (3): 326-331; 1977.

Cultures of trypsinized chick embryo fibroblasts were inoculated with Sindbis virus, and the effect on endogenous oncornavirus production was determined. Sindbis virus enhanced the maturation and release of the oncornaviruses. Since Sindbis virus did not form phenotypically mixed virions with oncornavirus, it was concluded that the two are synthesized separately. (3 refs.)

- 77-6327 **The Influence of the Major Histocompatibility Locus on Marek's Disease in the Chicken.** (Eng) Stone, H. A. (Regional Poultry Res. Lab., U.S. Dept. Agriculture, Agricultural Res. Services, Northern Illinois Univ., DeKalb, IL); Briles, W. E.; McGibbon, W. H. *Adv Exp Med Biol* 88: 299-307; 1977.

Genetic studies of chickens were made to ascertain their susceptibility to Marek's disease. Chickens of genotypes lacking the B²¹ allele had significantly higher Marek's mortality (50% to 77%) than those of genotypes with B²¹ (0% to 9%). The inherited basis for the rapid acquisition of resistance to Marek's disease may be due to the increased frequency of the B²¹ allele. (15 refs.)

- 77-6328 **Marek's Disease Virus-induced Tumor Transplants: Development and Rejection in Various**

Genetic Strains (Meeting Abstract). (Eng) Fabricant, J. Ithaca, NY); Calnek, B. W.; Schat, K. A.; Murthy, K. K. *J Am Vet Med Assoc* 171(10): 1105; 1977. (no refs.)

- 77-6329 **Notes on the Mechanism of Postvaccination Immunity in Marek's Disease.** (Eng) Yakovleva, L. S. (Cancer Res. Center, Acad. Medical Sciences, 115478 Moscow, USSR); Mazurenko, N. P. *Neoplasma* 24(4): 389-394; 1977.

The 16th and 45th in vitro passages of a nonpathogenic variant (83) of the Kekava strain of Marek's disease virus induced resistance to Marek's disease when injected ip into chickens 14 days before injection of the pathogenic variant 55. Simultaneous administration of both variants did not protect chickens from the disease. Chicken fibroblast cultures were infected with blood cells from vaccinated chickens to study the interrelationship of the two variants in chickens. The results showed that with sequential administration, there was interference between the viruses, since the amount of the pathogenic variant isolated from blood cells was three times lower than that of the nonpathogenic variant. In addition, the viruses persisted in different cells. After simultaneous infection of chickens with both variants, however, equal amounts of each were isolated, and they persisted in the same cells. (11 refs.)

- 77-6330 **The RNA of Avian Acute Leukemia Virus MC29.** (Eng) Duesberg, P. H. (Dept. Molecular Biology, Univ. California, Berkeley, CA 94720); Bister, K.; Vogt, P. K. *Proc Natl Acad Sci USA* 74(10): 4320-4324; 1977.

The RNA of myelocytoma virus MC29, a replication-defective avian acute leukemia virus, was investigated to determine whether it has unique transforming sequences responsible for acute leukemia and transformation of tissue culture cells or whether it shares transforming sequences with avian sarcoma viruses. Sedimentation and electrophoretic analyses indicated that the virus contains a distinct 28S RNA with about 5,700 nucleotides. It is the smallest avian tumor virus RNA detected to date. The size of the RNA suggests that the defectiveness of the virus is due to deletions in replicative genes. The RNA shared 3 to 5 of 30 large RNase T₁-resistant oligonucleotides with the RNA of other avian leukosis and sarcoma viruses. Hybridization indicated that 61% of the viral RNA contains sequences in common with other avian sarcoma and leukosis viruses. At least 32% of the RNA (about 1,800 nucleotides) appears to be MC29-specific and may represent the transforming information of the virus. Sequences of the conserved transforming gene of avian sarcoma viruses were not detected in MC29 RNA. It is concluded that the transforming sequences of MC29 RNA define a new class of avian tumor virus transforming genes. (38 refs.)

77-6331 Horizontal Transmission of Feline Leukemia Virus under Experimental Conditions. (Eng)

Hoover, E. A. (Dept. Veterinary Pathobiology, Coll. Veterinary Medicine, Ohio State Univ., 1925 Coffey Road, Columbus, OH 43210); Olsen, R. G.; Hardy, W. D.; Schaller, J. P. *J Natl Cancer Inst* 58(2): 443-444; 1977.

Thirty-seven specific-pathogen-free cats ranging in age from newborn to 12 mo were inoculated ip with 10^5 focus-forming units of Rickard strain feline leukemia virus (FeLV). Each cat then shared a cage with an uninoculated control for 40 wk postinoculation. All animals were monitored biweekly for the presence of group-specific antigen (gsa) and for virus-neutralizing (VN) and feline oncornavirus-associated cell membrane antigen (FOCMA) antibody titers. After 4-5 wk, 20 cats became persistently viremic (gsa-positive). The other 17 remained gsa-negative but developed VN and FOCMA titers ≥ 1.8 . Seventeen of the control cats in contact with the gsa positive cats developed FeLV infection 4-18 wk (mean 10.5 wk) after viremia was first detected in their inoculated cage mates. Four of these control cats became gsa-positive, and the other 13 developed both VN and FOCMA antibodies. None of the 17 control cats that were caged with the 17 gsa-negative inoculated cats developed evidence of infection. It is concluded that after ip inoculation of cats with FeLV, the gsa-positive or viremic state correlates with the capacity for contagious or horizontal transmission of the virus. Transmission probably involves close physical contact or the use of common feeding apparatus or litter containers, as opposed to airborne transmission. (9 refs.)

77-6332 Detection of Bovine Leukemia Virus in B-Lymphocytes by the Syncytia Induction Assay. (Eng)

Paul, P. S. (Dept. Large Animal Clinical Sciences, Coll. Veterinary Medicine, Univ. Minnesota, St. Paul, MN 55108); Pomeroy, K. A.; Castro, A. E.; Johnson, D. W.; Muscoplat, C. C.; Sorensen, D. K. *J Natl Cancer Inst* 59(4): 1269-1272; 1977.

Peripheral blood lymphocytes (PLB), obtained from three Jersey cows with persistent lymphocytosis and one Holstein steer infected at birth with bovine leukemia virus (BLV), were separated on nylon wool columns into adherent and nonadherent populations. The nylon-adherent cells were enriched in B-lymphocytes, and the non-adherent fraction contained mostly non-B-lymphocytes. The PBL and the two separated were population assayed for the presence of BLV by syncytia induction in bovine embryonic spleen culture. Generally, the PLB and B-lymphocyte populations produced many syncytia, while non-B-lymphocytes yielded few or no syncytia. The syncytia were neutralized by anti-BLV serum, and not by anti-bovine syncytial virus or control sera; furthermore, PBLs from normal control animals were negative for BLV syncytia induction. These results indicate that BLV is present in the B-lymphocyte presumably the target cell for the virus. These findings are consistent with earlier reports that viruses affect either B- or T-cells, but never both. (29 refs.)

77-6333 Visna Virus RNA Synthesis. (Eng.) Brahic, M. (Univ. California, San Francisco, Veterans Admin. Hosp., San Francisco, CA 94121); Filippi, P.; Vigne, R.; Haase, A. T. *J Virol* 24(1): 74-81; 1977.

A molecular analysis was conducted of the RNA products of visna virus in sheep choroid plexus cells. The fate of parental RNA, the time course of progeny RNA synthesis, and the sizes of different intracellular RNAs were examined. (21 refs.)

77-6334 The Relationship Between Age-dependent Immunological Competence of Host and Tumor Growth in the Hamster-Bovine Adenovirus Type 3 System. (Eng) Motoi, M. (Dept. Pathology, Okayama Univ. Medical Sch., 2-5-1 Shikata-cho, Okayama 700, Japan); Ohmori, H.; Ogawa, K. *Acta Pathol Jpn* 27(4): 463-473; 1977.

The relationship between age-dependent immunological maturation in Syrian golden hamsters and bovine adenovirus type 3 (BAV-3, strain WBR-1) carcinogenesis was investigated. The animals received different sc doses of virus (titer, $10^{4.5}$ TCID₅₀/0.1 ml) according to age. The age of the animals at inoculation (and dose) was 1 day (0.1 ml), 1 wk (0.2 ml), 2 wk (0.2 ml), 3 wk (0.3 ml), 30 days (0.5 ml), 3 mo (0.5 ml), and 1 yr (0.5 ml). Tumor incidence was 100% in animals inoculated at 1 day and 1, 2, and 3 wk, 75% for those inoculated at 30 days, 86% at 3 mo, and 80% at 1 yr; there was no sex difference. The latent period increased with age. Tumor growth was progressive in young animals and mainly static or regressive in those inoculated at 3 wk or later. The histology of the tumors is presented. Plaque-forming cells (PFC) were first noted at 12 days of age, and they increased with age to approx 100 PFC/spleen in adults. An increase in immune PFC above the normal level was detected in animals immunized at 1 wk. Max antibody-forming capacity was noted when the hamsters were 6 mo old. Development of serum hemagglutinin and hemolysin responsiveness was similar to that of PFC responsiveness. Transplantation immunity did not develop in animals immunized with BAV-3 at birth, but it developed strongly in animals immunized at 30 days. Tumor growth was accelerated in the animals immunized at 3 wk as a result of antithymocyte serum administration, thymectomy, and inoculation of x-irradiated tumor cells. BCG inhibited progressive tumor growth in animals inoculated at birth, as did repeated inoculation of excess doses of BAV-3 and transfer of sensitized lymphocytes during tumor latency. Spleen cells from progressive and nonprogressive tumors inhibited colony formation of BAV-3 hamster tumor cells. Blocking activity to sensitized lymphocytes was demonstrated in sera from hamsters developing progressive tumors early in carcinogenesis. Tolerance to tumor-specific transplantation antigens did not play an important role. (33 refs.)

77-6335 Mouse Adenovirus: Growth of Plaque-purified FL Virus in Cell Lines and Characterization of

Viral DNA. (Eng) Larsen, S. H. (Dept. Microbiology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD); Nathans, D. *Virology* 82(1): 182-195; 1977.

Experiments with adenovirus FL (AdFL), isolated from Swiss mouse cells, were designed to test its host range, to develop a procedure for preparing virions and viral DNA suitable for genetic and biochemical study, to characterize the viral DNA, and to establish cleavage maps of the viral genome. AdFL was found to be a typical adenovirus, based on virion morphology, the properties of its DNA, and its limited host range (it only grows in murine cells). AdFL DNA is a linear duplex with a mol wt of 20×10^6 , similar to human adenoviruses. Furthermore, AdFL appears to have protein covalently linked to its ends. In contrast to human adenovirus strains, however, the base composition of AdFL DNA is significantly lower, having little or no ($< 10\%$) nucleotide sequence homology with representative strains of human adenoviruses (Ad12 of Group A, Ad7 of Group B, and Ad2 of Group C). There was reactivity between extracts of AdFL-infected cells and antiserum against human adenovirus, but sera directed against the T antigens of adenoviruses from Groups A, B, and C did not react with AdFL-infected cell lysates. Cleavage maps of AdFL DNA were constructed by the use of six restriction endonucleases. These maps differed from those of Ad2 or Ad5. (29 refs.)

77-6336 Morphology of the Guinea Pig Leukemia Associated Viruses. (Eng.) Vernon, M. L. (Microbiological Associates, Bethesda, MD 20016); Knipscher, R. C.; More, N. S.; Ruch, D. G.; Green, I.; Rhim, J. S. *Fed Proc* 36(9): 2297-2304; 1977.

Morphological characterization of the guinea pig leukemia-associated viruses led to the term guinea pig retravirus being used for the non-herpes-type virus particles that share some features in common with A-, B-, and C-type particles. The mature extracellular guinea pig retravirus is approx 100 nanometers (nm) in diameter, has a rough outer surface with irregular projections, a very dense layer just under the outer limiting membrane, a dense, poorly defined, nucleoid region that is often eccentric, and it usually displays a tail. Negative staining reveals spikes on the surface. Budding and free immature particles are rare. Intracytoplasmic A particles are approx 70 nm in diameter and appear to be the nucleoid of budding particles. Particles within and budding into the cisterna of the rough endoplasmic reticulum are either large (90-nm) particles with four layers or, less frequently, 70-nm doughnut-shaped particles lacking the outer layer. Extracellular mature particles and intracytoplasmic particles are most evident in chemically induced cultured cells, from either normal tissues or nonproducer clones from guinea pig embryo cells transformed by Kirsten murine sarcoma virus. Intracisternal particles were found in cultured L₂C lymphoblasts and in cultured tissues from leukemic, but not normal, animals. (34 refs.)

77-6337 Characterization of Bromodeoxyuridine-induced Guinea Pig Type B Retravirus. (Eng.) Putman, D. L. (Microbiological Associates, Bethesda, MD 20016); Rhim, J. S. *Fed Proc* 36(9): 2316-2319; 1977.

Recent studies of bromodeoxyuridine (BUdR)-induced guinea pig retravirus are reviewed. The spontaneous release of B-type guinea pig virus from a long-term culture of strain 13 guinea pig tumor cells induced by Kirsten murine sarcoma virus (Ki-MSV) is described. Nonproducer guinea pig embryo clone 12 cells isolated from transformed foci induced by Ki-MSV did not demonstrate murine leukemia virus antigens or produce an infectious virus. However, they were morphologically indistinguishable from virus-releasing murine sarcoma virus-transformed guinea pig embryo lines and produced tumors in newborn guinea pigs. The time course of induction of reverse transcriptase in the culture fluid of nonproducer cells exposed to BUdR for 24 hr showed peaks 6-8 days after treatment. The polymerase activity in the BUdR-induced guinea pig retravirus was characterized by two techniques. The virus concentrate was tested in a poly(rA):oligo(dT)-templated DNA polymerase assay utilizing several MgCl₂ or MnCl₂ concentrations, and incorporation of ³H-thymidine 5'triphosphate into the template-primers poly(rA):oligo (dT) and poly(dA):oligo(dT) was compared. (26 refs.)

77-6338 Malignant Transformation of Rat Embryo Cells by a Herpesvirus Isolated from L₂C Guinea Pig Leukemia. (Eng) Rhim, J. S. (Dept. Cancer Res., Microbiological Associates, Inc., Bethesda, MD 20016). *Virology* 82(1): 100-110; 1977.

The biological characteristics of a guinea pig herpesvirus (GPHV) isolated from mink lung cells (Mv 1 Lu) after cocultivation with L₂C leukemic cells are described, and the in vitro malignant transformation of rat embryo cells by this virus is reported. The morphological and biochemical characteristics of the GPHV were considered to be very similar to those of Epstein Barr virus found in Burkitt's lymphoma, but different from guinea pig cytomegalovirus. Complement-fixing antigen for human herpes simplex type 1 virus was detected in cell suspensions prepared from GPHV-infected mink cells. This is the first reported evidence of an antigenic relationship between GPHV and other herpesviruses. The host range of GPHV was found to be narrow. The GPHV-transformed rat cells had properties generally associated with viral transformation, including altered morphology and tumorigenicity in syngeneic animals. The transformed cells produced neither viral antigen nor a rescuable infectious virus; however, they were positive for human herpes simplex virus type 1 complement-fixing antigen but negative for infectious virus. This in vitro transformation system using GPHV-induced rat tumors may make it possible to identify a specific T-antigen. Additional studies on virus-specific transplantation antigens induced by GPHV may be possible through this system. (28 refs.)

- 77-6339 **The Spontaneous Release of Endogenous Rat Type-C Virus from Myogenic Cells in Culture** (Meeting Abstract.) (Eng.) Bendas, C. M. (Dept. Microbiology and Immunology, Hahnemann Medical College, Philadelphia, PA 19102); Crowell, R. L.; Goldberg, R. J. *In Vitro* 13(3): 172-173; 1977. (no refs.)

- 77-6340 **Quantitative Determination of Transformed Cells in a Mixed Population by Simultaneous Fluorescence Analysis of Cell Surface and DNA in Individual Cells.** (Eng.) Hawkes, S. P. (Lab. Chemical Biodynamics, Univ. California, Berkeley, CA 94720); Bartholomew, J. C. *Proc Natl Acad Sci USA* 74(4): 1626-1630; 1977.

A technique for distinguishing between transformed and non-transformed Balb 3T3 A31 cells is described. Cell-surface labeling with fluorescamine and propidium iodide is combined with flow microfluorometry. This distinction can be revealed in cells transformed by RNA virus, DNA virus, and benzo[a]pyrene and therefore appears to be a general property of transformation. (17 refs.)

- 77-6341 **Morphology of Transplanted RNA Virus-producing Tumors. Light and Electron Microscopic Studies of Models of Isologous Transplanted Mammary Carcinomas, Sebaceous Gland Tumors, and Leukemia of the Laboratory Mouse.** (Ger.) Fasske, E. (Pathologischen Abteilung des Forschungsinstitutes Borstel, Parkallee 41, 2061 Borstel, W. Germany). *Fortschr Med* 95(12): 799-800; 1977.

Virus replication in mouse tumors that are comparable with corresponding human tumors was studied electron microscopically and biochemically. Virus synthesis in the tumor cells was not dependent on tumor age. The virus was found in spontaneous tumors, transplanted tumors, and leukemia. Malignant transformation of a cell by an oncornavirus is discussed. (no refs.)

- 77-6342 **Virus Particles in Ovarian Tumors of ddY/F Mice Exposed to X-Rays During Early Postnatal Life.** (Eng.) Komuro, M. (Zoological Inst., Faculty Science, Univ. Tokyo, Tokyo, Japan). *J Fac Sci Univ Tokyo Sect 4* 13(4): 417-422; 1976.

Quantitative studies were made of RNA tumor viruses in the irradiated ovaries of ddY/F and C3H/Tw mice using electron microscopy. The animals were irradiated with 130 R of x-rays at 2 wk of age and sacrificed at various times after irradiation. Four types of virus particles were identified: intracisternal A- (IAP), intracytoplasmic A- (CAP), B parti-

cles, and C particles. CAP and budding B and C particles (BP) were present exclusively in the interstitial and luteoma cells of the ddY/F mice. The number of interstitial cells containing these particles increased after 3 mo and became particularly high 18 mo after irradiation. Interstitial cells with BP were rarely observed in mice until 12 mo. The incidence of BP, however, markedly increased 18 mo after irradiation. In nonirradiated controls, BP were absent during the entire experimental period. Four luteomas and four nontumorous ovaries of ddY/F mice were examined 18 mo after irradiation to determine the difference in the number of cells bearing virus particles. All the luteomas had several BP. There were mature-type B particles, but no mature-type C particles were seen. Three of the four nontumorous ovaries did not contain BP. The high incidence of BP in all the luteomas suggests a close relationship between BP and their development. (10 refs.)

- 77-6343 **Segregation of Genetic Information for a B-tropic Leukemia Virus with the Structural Locus for BALB:Virus-1.** (Eng.) Robbins, K. C. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD 20014); Cabradilla, C. D.; Stephenson, J. R.; Aaronson, S. A. *Proc Natl Acad Sci USA* 74(7): 2953-2957; 1977.

The origin of the B-tropic leukemia virus of BALB/c mice was investigated. Analysis of individual NIH x (NIH x BALB)F₁ backcross generation embryo cellular DNA's for genetic sequence homology with BALB:virus-1 defined its relationship to previously identified BALB/c inducibility loci. This suggests that information of the B-tropic virus is encoded in the genome closely linked to the structural locus for BALB:virus-1. The evidence indicates that a small genetic alteration in BALB:virus-1 leads to a virus whose growth is unrestricted and, subsequently, to the development of neoplasia. (43 refs.)

- 77-6344 **RNase T1-resistant Oligonucleotides of B-tropic Murine Leukemia Virus from BALB/c and Five of Its NB-tropic Derivatives.** (Eng.) Faller, D. V. (Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA 02139); Hopkins, N. *J Virol* 23(1): 188-195; 1977.

Fingerprinting by two-dimensional gel electrophoresis of the RNase T1-resistant oligonucleotide of five NB-tropic derivatives of a B-tropic murine leukemia virus (WN1802B) from BALB/c mice revealed great similarities. The B- and NB-tropic viruses apparently have 33/35 large T1-resistant oligonucleotides in common. All five of the NB-tropic viruses possessed a common alteration relative to their B-virus progenitor. It involved the acquisition of one oligonucleotide and, tentatively, the loss of one oligonucleotide. It was suggested that these alterations observed in NB-tropic viruses

may be related to the genetically stable change from B- to NB-tropism. (22 refs.)

- 7-6345 **In Vivo Interaction Between RNA Viruses Isolated from the C57BL/Ka Strain of Mice.** (Eng.) Decleve, A. (Cancer Biology Res. Lab., Dept. Radiology, Stanford Univ. Sch. Medicine, Stanford, CA 94305); Lieberman, M.; Kaplan, H. S. *Virology* 81(2): 270-283; 1977.

Radiation leukemia virus (RadLV) isolated from radiation-induced thymic lymphomas of C57BL/Ka mice has been shown to be thymotropic (T+) and leukemogenic (L+). Three other classes of endogenous viruses of strain C57BL/Ka mice have been shown to be devoid of thymotropic or lymphomagenic activity (T-L-). The isolates designated BL/Ka(B), BL/Ka(N), and BL/Ka(X) have been characterized as homogeneous, typical B-, N-, and X-tropic preparations, respectively. However, three other isolates, RadLV, RadLV-LTC, and BL/Ka(6), were found to be mixtures of viruses, containing relatively small amounts of a xenotropic virus serologically and biologically equivalent to BL/Ka(X); but their major components were quite different. The major component of BL/Ka(6) was a B-tropic, ecotropic virus apparently indistinguishable from BL/Ka(B). In contrast, the major component of RadLV and RadLV-LTC was found to be serologically distinct from all of the other viruses studied and uniquely capable of infecting and replicating to high titer in C57BL/Ka mouse thymocytes. This thymogenic component, also highly leukemogenic, was designated T+ L+. It was suggested from coinfection studies that BL/Ka(6) and RadLV-LTC contained attenuated or defective TL particles that were susceptible to the enhancing action of the non-thymotropic viruses. (32 refs.)

- 7-6346 **Genetic Studies in the Resistance of Mice to Radiation Leukemia Virus (Meeting Abstract).** (Eng.) Lonai, P. (Weizmann Inst. Science, Rehovot, Israel); Haran-Ghera, N. *Isr J Med Sci* 13(10): 1061-1062; 1977. (no refs.)

- 7-6347 **Reovirus-specific Enzyme(s) Associated with Subviral Particles Responds In Vitro to Polyribocytidylate to Yield Double-stranded Polyribocytidylate-Polyriboguanilate.** (Eng.) Gomatos, P. J. Sloan-Kettering Memorial Cancer Center, New York, NY 10021; Kuechenthal, I. *J Virol* 23(1): 80-90; 1977.

Reovirus-specific particles sedimenting from 300S to 550S were isolated from the cytoplasm of reovirus-infected mouse L cells. These particles have an enzymatic activity capable of synthesizing polyriboguanilate [poly(G)] on a polyribocytidylate [poly(C)] template.

Other than a previously identified polyriboadenylic acid [poly(A)] polymerizing activity that was present at a low level in these fractions, no additional polymerizing activity was found when the homopolymers poly(G), poly(A), polyuridylate, or 2'-O-methyl-poly(C) were tested as templates. Optimal poly(G) synthesis occurred in the presence of Mn^{2+} with poly(C) as template; however, the addition of guanylyl (3' to 5')-guanosine (GpG) as primer greatly stimulated the synthesis of poly(G) in the presence of Mg^{2+} , but not Mn^{2+} . Particles with replicase and transcriptase activity reached their max amounts in infected cells between 15 and 18 hr after infection. Exponential increase in particles with poly(C)-dependent polymerase activity began at 23 hr, with max amounts present at 31 hr, the time of onset of exponential virus growth. Thus, the decrease in particles with replicase and transcriptase activities coincided with the increase in poly(C)-responding particles. The relationship of the poly(C)-dependent polymerase to the reovirus was discussed. (43 refs.)

- 77-6348 **Comparative Expression of Virus Associated with Murine Plasmacytoma in Tumor Cells and in Mouse Embryo Cells.** (Fre.) Lemay, P. (Unite de Recherche de Virologie, INSERM, U. 102, 2, place de Verdun, 59045 Lille Cedex, France); Pluquet de Temmerman, N.; Tavitian, A. *CR Acad Sci [D] (Paris)* 284(24): 2573-2575; 1977.

A DNA complementary (cDNA) to the viral genome of C-type particles produced by a mouse myeloma-derived cell line (MF₂) was used as a probe to study viral genome expression among total RNA and poly(A)-rich RNA extracted from MF₂ and BALB/c mouse embryo cells. Only cDNA fractions with a sedimentation constant > 4S were used in the hybridization experiments. The level of association of a constant quantity of tritiated cDNA with growing quantities of cellular RNA was determined by measuring the degree of resistance of the probe to hydrolysis by S-1 nuclease. Molecular hybridizations were performed in calibrated pipettes at 68°C for 72 hr in a Tris buffer solution (0.01 M, pH 7.4) at a final volume of 200 µl. The total RNA extract of MF₂ cells hybridized more rapidly and more effectively (100%) with this probe than with the total RNA extract of embryonic fibroblasts (70%). The max level of hybridization obtained with poly(A)-RNA extracts of embryonic fibroblasts was 27%, whereas the same quantity of poly(A)-RNA extracts of the MF₂ cell line totally protected the probe from the effect of S-1 nuclease. The results suggest the presence of at least one endogenous BALB/c virus in MF₂ cells. (8 refs.)

- 77-6349 **Study of the Replication of a C-type Murine Xenotropic Virus in Different Mammalian Cells. Definition of a Specific Antigen.** (Fre.) Blaineau, C.

(Laboratoire Immunologie et Virologie des Tumeurs, Hôpital Cochin, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France); Gisselbrecht, S.; Hurot, M. A.; Pozo, F. *CR Acad Sci [D]* (Paris) 284(D): 2427-2430; 1977.

A mink cell line was found to be especially susceptible to infection by the murine xenotropic virus AT 124. Furthermore, a specific cell-surface antigen was detected in the serum of (W/Fu x BN)_F rats hyperimmunized with AT 124 virus. (12 refs.)

77-6350 Detection and Quantitation of Phenotypically Mixed Viruses: Mixing of Ecotropic and Xenotropic Murine Leukemia Viruses. (Eng) Ishimoto, A. (Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH Bethesda, MD 20014); Hartley, J. W.; Rowe, W. P. *Virology* 81(2): 263-269; 1977.

Phenotypic mixing between ecotropic and xenotropic murine leukemia viruses (MuLV) occurred when both components of the mixed infection were exogenous, when one was endogenous and the other exogenous, and when both were endogenous. Systems for the production and quantitation of phenotypically mixed particles between ecotropic and xenotropic MuLV's are described. Phenotypically mixed particles having the genome of ecotropic MuLV and the host range determinant of xenotropic MuLV or particles having the genome of xenotropic MuLV with the host-range determinant of ecotropic MuLV were both found. Although phenotypic mixing between enveloped viruses involves surface glycoproteins, other viral proteins may also be involved. (17 refs.)

77-6351 Detection of Endogenous C-Type Viral Antigens During Development of Mice. (Rus.) Bogovskii, B. P. (Lab. Immunochemistry and Tumor Diagnostics, N. F. Gamaleia Inst. Epidemiology and Microbiology, Moscow, USSR); Lezhneva, O. M. *Biull Eksp Biol Med* 84(7): 72-75; 1977.

Expression of the mouse C-type virus major structural p30 protein (gs-1) and the Gross leukemia virus type-specific antigen (AGLV) was examined in embryonic (day 12-20), newborn and adult AKR and BALB/c mice by radioimmunodiffusion. The p30 protein was detectable in both lines from the 12th day of development through adult life. AGLV was not present in embryos of either line or in adult BALB/c mice; however, it was found in postnatal AKR mice after one or two days. These findings suggest that the p30 protein and the AGLV antigen are expressed independently. (13 refs.)

77-6352 Cellular Changes in the Thymuses of Preleukemic AKR Mice: Correlation with Changes in

the Expression of Murine Leukemia Viruses. (Eng) Nowinski, R. C. (Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle, WA 98104); Doyle, T. *Cell* 12(2): 341-353; 1977.

Thymus cells of preleukemic and leukemic AKR mice expressed elevated levels of antigens associated with the murine leukemia virus (MuLV) proteins gp70 and p30. Expression of the viral proteins varied quantitatively with age of the mouse and qualitatively with the cellular populations expressing the antigens. Antigen levels were low in 2-mo-old mice, and gp70 was expressed only on the surface of large subcapsular thymocytes. At age 6 mo, increases in p30 and gp70 levels paralleled the selective depletion of cortical thymocytes and the concomitant increase in the medullary region of the thymus. Some 8-mo-old mice demonstrated hypertrophy of a single thymic lobe, which contained cells intermediate in size between small cortical cells and leukemic blast cells. These cells did not induce tumors in syngeneic recipients, but they expressed elevated antigen levels. Thymocytes of mice with overt leukemia contained primarily leukemic blast cells that expressed extremely high antigen levels. These cells rapidly induced transplantable leukemias. The increases in viral antigen expression correlated with the increased production of infectious ecotropic and xenotropic MuLV in the thymus. (24 refs.)

77-6353 Spontaneous and Induced Appearance of Murine Leukemia Virus Antigen Containing Cells in Organ Cultures of Embryonic Mouse Thymus. (Eng) Riensfeld, I. (Dept. Virology, Inst. Medical Microbiology, Univ. Uppsala, Uppsala, Sweden); Alm, G. V. *Int J Cancer* 20(2): 309-317; 1977.

The potential usefulness of embryonic thymus organ cultures in studies of the relation of endogenous murine leukemia virus (MuLV) and the thymus to the development of lymphoma cells was evaluated. Thymuses from 14-day-old AKR and CBA embryos were used. Four main conclusions were drawn: (1) it was possible to sustain lymphopoiesis in long-term organ culture (at least 9 wk); (2) the spontaneous appearance of MuLV antigen-containing cells in long-term organ cultures occurred, but infrequently; (3) it was possible to infect embryonic thymuses and obtain the sustained presence of MuLV-containing cells in culture; (4) iododeoxyuridine treatment (20 µg/ml of culture for 24 hr) on culture days 0 or 3 induced a high frequency of endogenous MuLV and decreased the number of lymphocytes per thymus. These results indicate the potential usefulness of the organ culture system in studying leukemogenesis. (46 refs.)

77-6354 Oncornavirus Produced by Murine Leukemia Cells in Culture. (Eng.) Nowinski, R. C. (Fred Hutchinson Cancer Res. Center, 1124 Columbia St., Seattle,

WA 98104); Hays, E. F.; Doyle, T.; Linkhart, S.; Medeiros, E.; Pickering, R. *Virology* 81(2): 363-370; 1977.

Leukemia cells from high-leukemia-strains AKR and C58 mice produced murine leukemia viruses (MuLV) that were defective in inducing syncytia (XC⁻) in the XC plaque assay and had a low infectivity in mouse embryo fibroblasts. These viral isolates were oncogenic when injected into newborn AKR mice. In contrast, the viruses that occur in the tissues and serum of normal AKR mice were capable of inducing syncytial formation (XC⁺) in the plaque assay and were not oncogenic in vivo. The XC⁻ virus could undergo conversion to an XC⁺ phenotype by serial passage in culture. The production of XC⁻ MuLV prevented superinfection by XC⁺ viruses, and the relationship of this phenomenon to the development of leukemia in mice was discussed. It was concluded that the leukemogenic virus of AKR mice is distinct from the endogenous XC⁺ MuLV that occurs in high titer in these animals. (14 refs.)

77-6355 **Isolation and Characterization of a Subline of Friend Erythroleukemia Cells That Differentiate in Tissue Culture in the Absence of Inducers.** (Eng) Rovara, G. (Wistar Inst., 36th St. at Spruce, Philadelphia, PA 19104); Surrey, S. *Cancer Res* 37(11): 4211-4219; 1977.

Spontaneously differentiating clonal sublines were isolated from a clone (745) of undifferentiated Friend erythroleukemia cells. When cultured in the absence of any differentiation inducers, these clonal sublines contain a high percentage (up to 75%) of cells synthesizing Hb at different stages of erythroid differentiation. One subclone, clone D, was characterized in more detail. Its stem cells could not be superinduced to differentiate by dimethyl sulfoxide, butyric acid, or hypoxanthine; variations in serum and glucose concentration had little effect on the percentage of benzidine-positive cells or the amount of Hb synthesized in the cultures. The differentiating cells averaged a max of six cell divisions. The globin chain composition of spontaneous differentiating clone D cells differed from that of induced cells of the parental clone. The β -minor but not the β -major chain could be identified; the β/α chain ratio was in favor of α . The ratio between histone H-2a1 and H2a2 was different from that of the parental clone and resembled that of a noninducible, non-differentiating clone, R₁Z. The phenotype of clone D was not stable. An increase in the number of stem cells that could not differentiate caused a progressive evolution of the clone toward a population containing progressively fewer (5%-10%) benzidine-positive cells. However, stem cells with a high potential for differentiation could always be rescued by subcloning. (37 refs.)

77-6356 **Antigenic Modulation of Friend Virus Erythroleukemic Cells In Vitro by Serum from Mice with Dormant Erythroleukemia.** (Eng.) Genovesi, E.

V. (Dept. Microbiology, Thomas Jefferson Univ., Philadelphia, PA 19107); Marx, P. A.; Wheelock, E. F. *J Exp Med* 146(2): 520-534; 1977.

Friend leukemia virus (FLV) induced erythroleukemia in mice can be suppressed to a dormant state by treatment with statolon. The host mechanisms involved in maintaining FLV in a dormant state were analyzed. Serum from mice with dormant FLV infections contains antibodies against FLV virion polypeptide and is cytotoxic for FLV-transformed cells; this serum is designated dormant FLV-immune serum (FVIS). When FLV leukemia cells (FLC-745) were cultured in the presence of FVIS (but in the absence of complete complement), there was a reversible modulation of FLV cell-surface antigens. FLC-745 cells cultured in FVIS became resistant to complement-mediated cytotoxicity by FVIS, but regained their susceptibility when cultured in normal mouse serum. Membrane immunofluorescence studies revealed that FLC-745 cells cultured in FVIS undergo formation of FLV-specific antigen-antibody complexes. These complexes are initially distributed evenly over the surface of the cells, but are redistributed by patching, then capping, followed by the loss of FLV-specific immune complexes. There was a temporal relationship between the redistribution and loss of FLV antigen-antibody complexes and decreased cell susceptibility to cytotoxicity by FVIS. The relationship of antigenic modulation of FLV erythroleukemic cells to inhibition of FLV genome expression in vivo and maintenance of the tumor dormant state is discussed. (50 refs.)

77-6357 **"gag" Polypeptide Precursors of Rauscher Murine Leukemia Virus.** (Eng.) Arcement, L. J. (Dept. Biology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Karshin, W. L.; Naso, R. B. *Virology* 81(2):284-297; 1977.

¹⁴C-labeled amino acid pulse-chase experiments on Rauscher murine leukemia virus (R-MuLV)-infected mouse cells identified several unstable precursor polypeptides: Pr1a+b (approx 200,000, or 200K, daltons), Pr2a+b (90K), Pr3 (80K), Pr4 (65K), Pr5 (55K), and Pr6 (45K). Pr1, Pr5, and Pr6 are present in cells in relatively small amounts compared to Pr2, Pr3, and Pr4. The major polypeptide precursors of the four internal structural proteins of R-MuLV, designated p30, p15, p12, and p10 (collectively termed the "gag" proteins), were examined with antigag sera. Monospecific antisera prepared against R-MuLV p30, p15, p12, and p10 recognized the precursors Pr1a+b, Pr3, Pr4, and Pr5 in immune precipitation reactions. Pr1a+b was previously shown to contain reverse transcriptase antigenic determinants. Comparison of tryptic peptide sequences of the gag precursors and of the gag proteins indicated that p30, p15, p12, and p10 were present in Pr3 and Pr4. Other results suggested that Pr3 is a precursor to Pr4. It was concluded that (1) Pr3 and Pr4 contain all of the gag proteins, (2) Pr5 contains the p30, p15, and p12 peptide sequences and may contain the p10 sequences, and

(3) Pr6 contains the p30 and p12 sequences but lacks the p15 sequences. (23 refs.)

- 77-6358 **Murine Leukemia Virus Morphogenesis: Cleavage of P70 In Vitro Can Be Accompanied by a Shift from a Concentrically Coiled Internal Strand ("Immature") to a Collapsed ("Mature") Form of the Virus Core.** (Eng.) Yoshinaka, Y. (Worcester Foundation Experimental Biology, Incorporated, 222 Maple Ave., Shrewsbury, MA 01545); Luftig, R. B. *Proc Natl Acad Sci USA* 74(8): 3446-3450; 1977.

A method was devised for separating the immature and mature cores of Rauscher leukemia virus (RLV), and the cores were characterized morphologically and biochemically. RLV was exposed to a low concentration of Nonidet P-40 (NP40) detergent followed by sucrose gradient centrifugation to yield immature virus cores. These cores had a diameter of 920 Å, possessed knoblike protuberances, and contained a concentrically coiled internal strand apposed to the shell. The two major polypeptide components of the immature cores were p30, a 30,000-dalton group-specific antigen, and a polypeptide that had the size and antigenic characteristics of p70, the 70,000-dalton precursor protein of the group-specific antigens of murine leukemia virus. Mature cores were obtained as the major core structure when RLV was exposed to high NP40 concentrations. These cores had a diameter of 850 Å, a smooth proteinaceous perimeter, and a collapsed internal strand; they contained predominantly p30. Treatment of RLV with low levels of NP40 for 16 hr at 22°C yielded cores that showed a 70% decrease in the number of immature forms and a concomitant increase in the number of mature forms, a 60%-90% decrease of p70, and a 30% increase in a 40,000- to 42,000-dalton protein. These results suggest that maturation of RLV cores is accomplished by cleavage of p70. It is suggested that p70 is arranged from the outside to the inside of coiled cores in the sequence NH₂-p15-p12-p30-p10-COOH. Cleavage of p70 would result in p15 remaining in the hydrophobic layer while p30 takes part in formation of the core shell and p10 associates with the viral RNA to form the ribonucleoprotein. (16 refs.)

- 77-6359 **Effects of Streptovaricins and Their Degradation Products on RNA-directed DNA Polymerase of Rauscher Leukemia Virus.** (Eng.) Li, L. H. (Cancer Res., Upjohn Co., Kalamazoo, MI 49001); Cowie, C. H.; Gray, L. G.; Moran, D. M.; Clark, T. D.; Rinehart, K. L. *J Natl Cancer Inst* 58(2): 239-243; 1977.

The effects of streptovaricin complexes, streptovaricins, streptovals, and streptovaricin degradation products on the RNA-directed DNA polymerases (RDDP) of Rauscher leukemia virus (RLV), DNA-dependent DNA polymerases (DNA polymerases) of bacterial and mammalian cells, and

DNA-dependent RNA polymerases (RNA polymerases) of mammalian origin were investigated. The effects of streptovaricin complexes on the viral DNA polymerases varied significantly from lot to lot. All the streptovals and streptovaricin degradation products except varicinal A showed 2- to 10-fold improvement in activity against the viral enzyme over the parent streptovaricins. None of these compounds displayed any significant effect on either the DNA polymerase of L1210 leukemia cells and *Escherichia coli* or the RNA polymerase of isolated nuclei of mouse liver. Streptovals and several streptovaricin modification and degradation products that showed marked anti-RDDP activity over the parent streptovaricin and little or no effect on the other DNA and RNA polymerases were selected for further evaluation. (40 refs.)

- 77-6360 **Intracistronic Mapping of the Murine Type C Viral gag Gene by Use of Conditional Lethal Replication Mutants.** (Eng.) Reynolds, R. K. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD 20014); Stephenson, J. R. *Virology* 81(2): 328-340; 1977.

Mammalian RNA C-type viruses contain the gag gene, which codes for a 67,000 mol wt precursor polypeptide that undergoes posttranslational cleavage to give rise to viral structural proteins with mol wts of 30,000, or 30K (p30), 15K (p15), 12K (p12), and 10K (p10). Isolation and characterization of the intermediate cleavage products of the gag precursor polypeptide from cells infected by mutants of Rauscher murine leukemia virus (R-MuLV) with temperature-sensitive defects in maturation and assembly allowed the ordering of cleavage products. The sequence of the R-MuLV gag gene product was determined to be (5')-p15-p12-p30-p10(3'). (43 refs.)

- 77-6361 **The Effect of Interferon on De Novo Infection of Moloney Murine Leukemia Virus.** (Eng.) Wong, P. K. (131 Burrill Hall, Dept. Microbiology, Univ. Illinois, Urbana, IL 61801); Yuen, P. H.; MacLeod, R.; Chang, E. H.; Myers, M. W.; Friedman, R. M. *Cell* 10(2): 245-252; 1977.

Mouse TB cells (mixed bone marrow/thymus origin) infected with Moloney leukemia virus and treated with interferon were studied by scanning and transmission electron microscopy and temperature shift investigation. In interferon-treated cells there was at least a 1,000-fold decrease in virus production, but only a 10- to 20-fold decrease in the level of viral-specific extracellular reverse transcriptase activities, and only a 2- to 3-fold decrease in the number of virus particles seen on the cell membrane. While interferon did not appear to inhibit the late stages of virion assembly nor to prevent virion release, most of the extracellular virions in interferon-treated cells were noninfectious. (27 refs.)

77-6362 **Rapid Metabolism of Moloney Leukemia Virus Precursor Polypeptides in Virus Infected Swiss Mouse Embryo Cells.** (Eng.) Shanmugam, G. (Inst. Molecular Virology, St. Louis Univ. Sch. Medicine, St. Louis, MO 63110). *Biochem Biophys Res Commun* 78(2): 517-524; 1977.

The biogenesis of p30 and gp71, two Moloney murine leukemia virus proteins of the *gag* and *env* genes, was examined in newly infected mouse cells. Four polypeptides (88,000, 72,000, 62,000, and 39,000 daltons) were identified as precursors of p30, and one large polypeptide was detected as specific for gp71. These precursors were rapidly processed in this system. (16 refs.)

77-6363 **A Large Glycoprotein of Moloney Leukemia Virus Derived from Interferon-treated Cells.** (Eng.) Chang, E. H. (Lab. Experimental Pathology, Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, Bethesda, MD 20014); Friedman, R. M. *Biochem Biophys Res Commun* 77(1): 392-398; 1977.

Moloney murine leukemia virus (M-MuLV) produced in interferon-treated TB cells (a fibroblast cell line established from mixed cultures of thymus and bone marrow CFW/D mouse cells) has a low infectivity. A large glycoprotein (gp85) with a mol wt of 85,000 was found to be a prominent constituent of this virus, but it occurred only in trace amounts in virus derived from control TB cells. It was speculated that gp85 might be related to a glycoprotein precursor of the major viral glycoprotein gp69/71. Thus, one effect of interferon treatment in this system may be to inhibit cleavage processing of a viral glycoprotein, resulting in decreased infectivity. (22 refs.)

77-6364 **Relationship Between Moloney Murine Leukemia and Sarcoma Virus RNAs: Purification and Hybridization Map of Complementary DNAs from Defined Regions of Moloney Murine Sarcoma Virus 124.** (Eng.) Dina, D. (Genetics Dept., Albert Einstein Coll. Medicine, New York, NY 10033); Beemon, K. *J Virol* 23(3): 524-532; 1977.

Using cross-hybridization techniques, complementary DNA (cDNA) fractions were prepared whose sequences were: (1) specific for regions of the Moloney murine sarcoma virus (Mo-MSV) 124 RNA genome or (2) common to Mo-MSV and Moloney murine leukemia virus (Mo-MLV). Specificity was tested by annealing the cDNA fractions to appropriate parental RNA's. To determine a map of the Mo-MSV genome, a 2- to 10-fold excess of polyadenylic acid-tagged RNA fragments fractionated into known sizes by sucrose gradient centrifugation was hybridized to the specific cDNA fractions. Annealing of an excess of Mo-MSV-RNA to an Mo-MSV-specific cDNA indicated that the Mo-MSV-

specific region, not shared with Mo-MLV, extends between 1,000 and 2,500 nucleotides from the 3' terminus. A cDNA common to the Mo-MSV and Mo-MLV genomes annealed to the viral sequences located between 2,500 nucleotides and the 5' end (about two-thirds of the Mo-MSV RNA genome), as well as the 3'-terminal 1,000 nucleotides, and to the 5'-terminal half of Mo-MLV. The Mo-MSV-specific region, which separates the two groups of common sequences, may play a role in transformation. (34 refs.)

77-6365 **Intratibial Moloney Sarcoma Virus-induced Osteosarcoma in the Rat: Tumor Incidence and Pathologic Evaluation.** (Eng.) Olson, H. M. (Dept. Pathobiology, Coll. Veterinary Medicine, 1925 Coffey Rd., Ohio State Univ., Columbus, OH 43212); Capen, C. C. *J Natl Cancer Inst* 58(2): 433-437; 1977.

Young New Zealand Black rats were inoculated intratibially with a partially purified preparation of Moloney murine sarcoma virus (M-MuSV) starting on day 1 after birth. The standard virus preparation (SVP: titered at 5.7-6.5 log focus-forming units/ml) was diluted 1:7 and given at a dose of either 0.025 or 0.05 ml in one or both legs. Up to 92% of animals inoculated on day 1 developed osteosarcomas after a short latent period of 10-12 days. The neoplasms were composed of a spectrum of well- to poorly differentiated osteoblasts, osteocytes, and osteoclasts. Budding of C-type viral particles was associated with tumor induction. The highest incidences occurred when inoculations were given during the first 5 days of life; inoculation of older rats resulted in significantly fewer tumors. Rats inoculated on day 4 (vs day 1) consistently developed more osteoproliferative bone tumors that were often associated with hypercalcemia, increased serum alkaline phosphatase, and elevated urinary hydroxyproline. (14 refs.)

77-6366 **Phosphorylation and Nucleic Acid Binding Properties of m1 Moloney Murine Sarcoma Virus-specific pP60gag.** (Eng.) Oskarsson, M. K. (Lab. DNA Tumor Viruses, Viral Oncology Program, NCI, Bethesda, MD 20014); Long, C. W.; Robey, W. G.; Scherer, M. A.; Vande Woude, G. F. *J Virol* 23(1): 196-204; 1977.

A 60,000-dalton polypeptide (pP60-gag), a major virion protein in the feline leukemia virus pseudotype of m1 Moloney murine sarcoma virus [m1MSV(FeLV)], was found to undergo phosphorylation and to have nucleic acid binding properties. Virion P60 was also found to contain the antigenic determinants of pp12 (the major phosphoprotein of most rodent, feline, and primate RNA tumor viruses). Both pp12 and P60 contain phosphoserine and phosphothreonine, and the ³²P-labeled phosphopeptides of P60 and pp12 have the same electrophoretic mobility. Virion P60 binds preferentially to single-stranded DNA and RNA in a competition filter binding assay. Cellular P60 is also phosphorylated and binds to sin-

gle-stranded DNA. Thus, immunoprecipitation of cellular extracts shows that P60 is phosphorylated in producer and nonproducer transformed cells, indicating that phosphorylation is independent of virus assembly. In addition, P60 from cytoplasmic extracts was retained on single-stranded DNA-Sepharose columns, showing that cellular P60 binds to DNA. (33 refs.)

- 77-6367 Expression of Murine Sarcoma Virus Genes in Uninfected Rat Cells Subjected to Anaerobic Stress.** (Eng) Anderson, G. R. (Dept. Microbiology, Sch. Medicine, Univ. Pittsburgh, Pittsburgh, PA 15261); Matovic, L. M. *Science* 197(4311): 1371-1374; 1977.

Exposure of uninfected Fischer rat embryo cells in culture to anaerobic conditions induced the transcription of RNA into two types of RNA sequences corresponding to the two principal constituents of rat-derived C-type sarcoma virus genomes. (1) The sequences were the specific rat cell types present in the Kirsten and Harvey murine sarcoma virus genomes (MSV rat), and (2) an endogenous C-type rat leukemia virus (RaLV). Concentrations of specific RNA sequences (MSV rat and RaLV) induced by the anaerobic conditions were > 100 times those of untreated cells. Cycloheximide and bromodeoxyuridine induced specific RNA sequence levels that were approx 5- to 15-fold those of controls. Thirty other chemical agents tested gave less than a twofold alteration in the concentration of either RNA. One possible explanation of these results was that the viral genes may allow the cells to respond to conditions of curtailed respiration by facilitating fermentation through coding for key enzymes in glycolysis or sugar uptake. (24 refs.)

- 77-6368 Cyclic AMP-induced Morphological Transformation of Cells Infected by Temperature-sensitive Mouse Sarcoma Virus. Expression of Transformation-associated Markers.** (Eng) Somers, K. D. (Dept. Microbiology and Immunology, Eastern Virginia Medical Sch., Norfolk, VA 23501); Weberg, A. D.; Steiner, S. *J Cell Biol* 74(3): 707-716; 1977.

Normal rat kidney (NRK) cells infected with a temperature-sensitive (ts) mutant of mouse sarcoma virus [NRK(MSV-lb)] were investigated to determine whether markers associated with the transformed phenotype are coordinately expressed after exposure to cyclic AMP (cAMP) at the restrictive temperature, which results in morphological transformation. Concanavalin A (Con A) agglutinability, hexose transport rate, and incorporation of ¹⁴C-fucose into fucolipid III (FL III) and fucolipid IV (FL IV) of the cells were examined. NRK cells transformed by wild-type MSV or NRK(MSV-lb) grown under permissive conditions were agglutinated by low concentrations of Con A and had relatively high maxi agglutination levels that were specifically

inhibited by α -methyl-D-mannoside. NRK(MSV-lb) cells grown under restrictive conditions were weakly agglutinated by Con A and exhibited reduced maxi agglutination levels. Treatment of NRK(MSV-lb) cells with cAMP at the restrictive temperature resulted in morphological transformation and a change in the pattern of ¹⁴C-fucose incorporation into FL III and FL IV to one comparable to that of NRK(MSV-lb) at the permissive temperature or to NRK cells transformed by wild-type MSV. cAMP treatment at the restrictive temperature resulted in no increase in Con A agglutinability or 2-deoxy-D-³H-glucose transport relative to mock-treated cultures. These results demonstrate that cAMP-induced morphological transformation and altered fucolipid composition of NRK(MSV-lb) cells are not correlated with alterations in hexose transport rate or Con A agglutinability. (39 refs.)

- 77-6369 Spin Label Study of Normal and Ki-MSV Transformed Rat Kidney Cell Membranes.** (Eng) Schara, M. ("J. Stetan" Inst., Univ. Ljubljana, Jamova 39, 61001 Ljubljana, Yugoslavia); Sentjurc, M.; Cotic, L.; Pecar, S.; Palcic, B.; Monti-Bragadin, C. *Stud Biophys* 62(2): 141-150; 1977.

The cell membranes of normal and Kirsten murine sarcoma virus (Ki-MSV)-transformed rat kidney cells were studied by electron paramagnetic resonance (EPR) with methyl ester spin labels to determine hydrocarbon chain ordering of the cell membrane phospholipids as well as free rotation in the temperature range 4-37 C. Using the methyl ester of 2-(3'-carboxypropyl)-2-undecyl-4,4-dimethyl-3-oxazolidinyloxy/(MeFASL) as a spin label, the EPR revealed that at > 32 C and < 8 C the ordering of both membranes is comparable, but in the intermediate, the transformed cell membranes are better ordered. The rotational correlation time for MeFASL suggested slower rotation of the phospholipids in the membranes of transformed cells. Studies with the sodium salt of MeFASL (NaFASL) revealed no differences in the ordering parameter for the normal and transformed cells. However, the spectral intensity of the NaFASL-labeled membranes decreased with time, indicating chemical reaction of the nitroxide group of the label. At 37 C, the decay rate was greater for transformed cells than for normal cells. These results suggest that the NaFASL molecules are distributed closer to the membrane hydrophilic-hydrophobic interface and that the MeFASL molecules are buried deeper in the membrane interior. (13 refs.)

- 77-6370 Synthesis of Type-C Virus Particles from Murine Cultured Cells Induced by Iododeoxyuridine. VI. Biosynthesis of Reverse Transcriptase.** (Eng.) Reitz, M. S. (Litton Bionetics, Inc., 7300 Pearl St., Bethesda,

20014); Wu, A. M.; Gallo, R. C. *Int J Cancer* 20(1): 7-74; 1977.

The effects of dexamethasone (dex) and/or interferon (IF) on the biosynthesis of reverse transcriptase (RT) in 5'-iodo-2'-deoxyuridine (IUdR)-induced BALB/3T3 cells nonproductively transformed with Kirsten murine sarcoma virus were studied. Dex stimulated the production of BALB virus-2 (v-2) and its Kirsten sarcoma virus pseudotype, but it did not increase the intracellular specific activity of RT to barely detectable levels. Simultaneous treatment of induced cells with both dex and IF resulted in a level of intracellular RT equal to that of cells treated with IUdR alone, even though extracellular v-2 production was approx fivefold lower. In contrast, neither compound affected the synthesis of N-tropic ALB virus-1, which is produced later (5-7 days) after IUdR treatment, nor was there any decrease in intracellular RT at this time. These results indicate that dex and IF have both translational (or pretranslational) and posttranslational effects on the production of xenotropic (v-2) murine C-type virus. (30 refs.)

77-6371 **Immunologic Studies of the Low Molecular Weight DNA Binding Protein of Murine Oncor-
viruses.** (Eng.) Long, C. W. (Viral Oncology Program, CI-Frederick Cancer Res. Center, Post Office Box B, Frederick, MD 21701); Berzinski, R.; Gilden, R. V. *Int J Cancer* 843-850; 1977.

A modified purification method was developed and applied to the isolation of low-mol-wt, highly basic DNA-binding proteins from Rauscher leukemia virus (RLV), woolly monkey C-type virus (WoLV), and mouse mammary tumor virus (MMTV). The method involved the sequential procedures of gel filtration in guanidine hydrochloride, DEAE-cellulose chromatography, and affinity chromatography on single-stranded DNA sepharose. The binding protein from RLV and WoLV was the fastest migrating of the virion proteins on sodium dodecyl sulfate-polyacrylamide gels and was designated p10. The binding protein from these two viruses was resolved into two bands by acid-urea electrophoresis, indicating that in these two viruses the binding protein exists as two slightly different charged forms. The DNA binding protein from MMTV corresponded to the second fastest migrating virion protein and had an estimated mol wt of 12,500; it gave one component on urea gels. Antibody to Rauscher virus p10 was species-specific in gel diffusion and complement-fixation tests and did not exhibit cross-reactivity with other virion proteins. Results of a previous study on the endogenous cat virus RD114 and feline leukemia virus combined with the results of this study suggest that these DNA-binding proteins may be ubiquitous in retraviruses. (19 refs.)

77-6372 **Relative Importance of Genotype and Type of
Mammary Tumor Virus on Mammary Tumori-**

genesis in Mice. (Eng.) Nagasawa, H. (Pharmacology Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan); Morii, S.; Tsubura, A.; Yanai, R. *Eur J Cancer* 13(10): 1119-1122; 1977.

The relative importance of genotype and type of mammary tumor virus (MTV) in determining the biological and morphological characteristics of mammary tumors appearing during reproductive states was studied in mice. GR/A and SHN females, their reciprocal F1 hybrids [(GR x SHN)F1 and (SHN x GR)F1], GR/A foster-nursed by SHN lactators (GR/SHN), and SHN foster-nursed by GR/A lactators (SHN/fGR) were force bred until the third to the fifth pregnancy, beginning at 60 days of age. In GR/A, both F1 hybrids, and GR/fSHN mice, mammary tumor incidence by the third pregnancy was 88%-100%. All tumors were pregnancy-dependent and almost all were diagnosed as plaques or mammary tumor type p. In SHN and SHN/fGR mice, however, mammary tumor incidence and the percentage of pregnancy-dependent tumors were very low and most tumors were adenocarcinoma. The numbers of tumors per mouse were 2.2-3.2 in the first four groups and about one in the last two groups. In view of the genotype(s) and type(s) of MTV of each group of mice, these results indicate that the relative importance of the factors for determining the characteristics of mammary tumors during reproductive states in mice is in the order GR-genotype, SHN-genotype, GR-type of MTV, and SHN type of MTV. (12 refs.)

77-6373 **The Major Structural Proteins of Murine Mammary Tumor Virus: Techniques for Isolation.** (Eng.) Dion, A. S. (Inst. Medical Res., Copewood St., Camden, NJ 08103); Williams, C. J.; Pomenti, A. A. *Anal Biochem* 82(1): 18-28; 1977.

Techniques for isolation of the major structural proteins of murine mammary tumor virus (MuMTV), a B-type RNA tumor virus, are reported. In one method, which allows the simultaneous purification of RNA-directed DNA polymerase and four major structural polypeptides (gp68, gp55, p28, and p12), virions are disrupted with a nonionic detergent (nonidet P-40), and the solubilized proteins are separated by ion-exchange chromatography on cellulose columns followed by molecular sieving chromatography. The second method, useful for the isolation of gp55, gp34, p28, and p12, involves the solubilization of the viral proteins with sodium dodecyl sulfate and chromatography on G-200. The detergent is removed in Dowex columns, and final purification is by molecular sieving chromatography. (19 refs.)

77-6374 **Characterization of Mouse Mammary Tumor Viruses Propagated in Heterologous Cells.** (Eng.) Howard, D. K. (Meloy Labs., Springfield, VA 22151);

Colcher, D.; Teramoto, Y. A.; Young, J. M.; Schlom, J. *Cancer Res* 37(8, part 1): 2696-2704; 1977.

Mouse mammary tumor viruses (MMTV) from three different strains of mice (C3H, RIII, and GR) were used to establish productive infections in feline and mink cell lines. The virions released by these cells competed completely in a radioimmunoassay for the major virion surface glycoprotein of MMTV (gp52), demonstrating that antigenic determinants of gp52 are viral-coded. Competitive molecular hybridization experiments indicated that the 60S-70S RNA's of MMTV's propagated in feline cells contained all the nucleic acid sequences found in 60S-70S RNA from MMTV synthesized by murine cells. The virion buoyant densities in sucrose and cesium chloride, virion sedimentation coefficient, divalent cation requirement of the virion DNA polymerase, and morphology of MMTV's synthesized in the heterologous cells were similar to those of MMTV's grown in murine cells. Cultures of MMTV-infected feline cells continuously released 0.1-1.0 μg virus/ 10^7 cells/day during the 60-wk observation period. No detectable feline or murine C-type viruses were produced by these cultures. The synthesis of MMTV by heterologous cells provides a source of MMTV free of contaminating murine cellular nucleic acids and antigens that should be useful in immunological and molecular biological studies. (28 refs.)

- 77-6375 **Interferon-Mediated Inhibition of Mouse Mammary Tumor Virus Expression in Cultured Cells.** (Eng.) Strauchen, J. A. (Lab. Pathology, NCI, Bethesda, MD 20014); Young, N. A.; Friedman, R. M. *Virology* 82(1): 232-236; 1977.

Interferon (10-100 IU/ml) caused a 5- to 10-fold inhibition of glucocorticoid-stimulated mouse mammary tumor virus expression in a muring mammary tumor cell line, Mm5mt/c₁. Possible mechanisms of action are discussed and compared with mechanisms reported for interferon inhibition of murine leukemia virus. (16 refs.)

- 77-6376 **Comparison of Mouse Mammary Tumor Virus-specific DNA in Inbred, Wild and Asian Mice, and in Tumors and Normal Organs from Inbred Mice.** (Eng.) Morris, V. L. (Dept. Bacteriology and Immunology, Univ. Western Ontario, London, Ontario N6A 5C1, Canada); Medeiros, E.; Ringold, G. M.; Bishop, J. M.; Varmus, H. E. *J Mol Biol* 114(1): 73-91; 1977.

The DNA related to the genome of mouse mammary tumor virus (MMTV) was measured in normal organs from laboratory, inbred, and Asian mice and in mammary tumors from laboratory mice by annealing MMTV cDNA (single-stranded DNA complementary to the mouse MMTV genome) to cellular DNA. Normal organs from most labora-

tory strains contained 5-9 copies of MMTV DNA per diploid cell, but GR mice, which transmit a virulent strain of MMTV genetically, contained 9-14 copies of viral DNA per cell. The number of copies of viral DNA in mammary tumors from RIII and BALB/cfC3H mice exposed to milk-borne virus ranged from that found in normal organs to 30 copies per cell. Wild mice and a subspecies of *Mus musculus* (*M. musculus molossinus*) contained half the number of copies of MMTV DNA found in laboratory mice. There were no significant differences among the viral nucleotide sequences in DNA from normal organs of all tested strains of *M. musculus* and from RIII mammary tumors. Two Asian species of mice (*M. caroli* and *M. cervicolor*) contained limited portions of the viral genome in their DNA. About 30% of MMTV cDNA annealed to *M. cervicolor* DNA; virus-related sequences were reiterated 30-50 times in this species, and they diverged from the viral sequences in proportion to the divergence between *M. musculus* and *M. cervicolor* unique-sequence DNA (3%-5%). About 10% of MMTV cDNA annealed to highly diverged sequences, which were reiterated 3-16 times in *M. caroli* DNA. These results suggest that MMTV DNA has been present in the germ line of *Mus* at least since the evolution of the Asian species (3-5 x 10^6 yr ago) and that it appears to evolve as fast as cellular unique-sequence DNA. (55 refs.)

- 77-6377 **BALB/3T3 Cells Infected by the ts3 Mutant of Polyoma Virus Fail to Accumulate Virus-specific Early RNA at the Nonpermissive Temperature.** (Eng) Cogen, B. (Tumor Virology Lab., Salk Inst., San Diego, CA 92112); Eckhart, W. *J Virol* 24(2): 701-703; 1977.

The accumulation of virus-specific early RNA was measured in BALB/3T3 cells infected by the ts3 mutant of polyoma virus by annealing cytoplasmic RNA from infected cells to the purified, radiolabeled, early strand of polyoma virus. Cells infected by the mutant failed to accumulate significant amounts of early RNA at 39 C, compared to cells infected with wild-type polyoma. The small amounts of early RNA that did accumulate were attributed to leakiness of the mutant. This failure is consistent with the mutant's failure to express viral functions during lytic infection at the nonpermissive temperature. (12 refs.)

- 77-6378 **Interactions of Polyoma and Mouse DNAs. IV. Time Course and Extent of Integration of Polyoma DNA into Mouse DNA During Lytic Infection.** (Eng.) Turler, H. (Dept. Molecular Biology, Univ. Geneva, 1211 Geneva 4, Switzerland). *J Virol* 23(2): 272-285; 1975.

The time course of covalent binding of polyoma viral DNA to density-labeled (HL) mouse DNA was followed in mouse embryo cells that had been grown prior to infection (20-40 plaque-forming units/cell) in the presence of 5-bromodeoxyuridine (BUdR). HL mouse DNA was separated

from free polyoma DNA by extraction with sodium dodecyl sulfate (SDS) and repeated cesium chloride (CsCl) isopycnic centrifugations, which purify HL mouse DNA until contamination with free parental polyoma DNA is below the limit of detection [0.5 genome equivalent (g.e.) cell]. In lytically infected BUdR-prelabeled mouse embryo cultures, polyoma DNA bound to HL mouse DNA that had been extracted by the SDS-CsCl procedure was first detected in small amounts (1-2 g.e./cell) at 10 hr after infection. In cultures incubated with medium containing thymidine ($\mu\text{g/ml}$), 4-6 g.e. of polyoma DNA per cell were detected at 14 and 18 hr after infection. Practically all viral DNA was bound to high-mol-wt HL mouse DNA. In cultures incubated with normal medium (no additions) and extracted 17-20 hr after infection, 20-50 g.e. of polyoma DNA per cell banded with HL mouse DNA. When DNA of one of these samples was subfractionated by SDS-salt precipitation prior to isolation of HL mouse DNA, 80% of the viral DNA banding at increased density was present in the low-mol-wt DNA fraction. Covalent binding of polyoma DNA to HL mouse DNA was demonstrated by alkaline CsCl density gradient centrifugation. It is concluded that early polyoma messenger RNA is transcribed from free parental viral DNA, that covalent linear integration is first detectable at the time when tumor antigen is synthesized, and that only a few copies become integrated between 0-18 hr after infection, when cellular and viral DNA replication starts in individual cells. (50 refs.)

77-6379 **Analysis of Polyoma Virus Nuclear RNA by Mini-blot Hybridization.** (Eng.) Birg, F. (U119 de l'Institut National de la Sante et de la Recherche Medicale, Marseille, France); Favaloro, J.; Kamen, R. *Proc Natl Acad Sci USA* 74(8): 3138-3142; 1977.

The size and sequence composition of virus-specific RNA extracted from the nuclei of mouse cells late during polyoma virus (large-plaque, strain A2) productive infection were studied by blot-hybridization of ^{32}P -labeled RNA fractionated on CH_3HgOH /agarose gels. Most (80%) of the polyoma virus nuclear RNA (nRNA) was found in the non-polyadenylated (poly(A)-)fraction. This poly(A)-viral RNA was heterogeneous in size, comprising molecules between 0.4 and 4 times the length of a complete transcript of polyoma DNA. Viral RNA of all sizes contained species that together hybridized to the entire polyoma genome, but sequences complementary to the late region were more abundant than sequences complementary to the early region in transcripts < 10-12 kilobases long. The results indicate that small RNA molecules greater than genome length are transcribed from normal polyoma virus DNA late during productive infection. (27 refs.)

77-6380 **Strand-specific Transcription of Polyoma Virus DNA Late During Productive Infection (Letter**

to Editor). (Eng) Flavell, A. J. (Imperial Cancer Res. Fund Labs., Post Office Box 123, Lincoln's Inn Fields, London WC2A 3PX, England); Kamen, R. *J Mol Biol* 115(2): 237-242; 1977.

Pulse-labeled RNA extracted from the nuclei of infected cells was hybridized to excess amounts of either E- or L-strand polyoma DNA in solution. L-strand-specific complementary RNA (cRNA) was used to measure the efficiency of hybridization and to test the DNA strand preparations for cross-contamination. At max, 70% of the cRNA was recovered as RNase-resistant hybrids after exhaustive annealing to excess L-strand DNA; 0.1% was recovered with E-strand DNA. RNA from the nuclei of mouse embryo cells labeled late during polyoma infection was annealed to E- or L-strand DNA. Viral DNA synthesis was first observed between 16 and 20 hr post-infection in the cell system used. Between 91% and 97% of the newly synthesized viral RNA labeled from 24 to 36 hr postinfection annealed to L-strand DNA. The fraction of total RNA synthesis that is polyoma-specific increased during late infection. At 24 hr postinfection, about 0.1% was complementary to the E strand and about 2.7% was complementary to the L strand. At 33 hr, the corresponding figures were 0.65% and 6.7%. The proportion of virus-specific RNA transcribed from the E strand varied from 4% to 9% during the same period. These results suggest that viral RNA is predominately transcribed from the L strand at late times after infection. (15 refs.)

77-6381 **Dissociation of Polyoma Virus by the Chelation of Calcium Ions Found Associated with Purified Virions.** (Eng) Brady, J. N. (Div. Biology, Kansas State Univ., Manhattan, KS 66506); Winston, V. D.; Consigli, R. A. *J Virol* 23(3): 717-724; 1977.

Purified polyoma virions were treated with the chelating agent ethyleneglycol-bis-N,N'-tetraacetic acid (EGTA), with its high affinity for Ca^{2+} , and the reducing agent dithiothreitol (DTT) to study in vitro dissociation of the virions, using the hemagglutination assay. The conditions for max dissociation involved incubation of the virions with 0.15 M NaCl, 10 millim EGTA, and 3 millim DTT using 0.01 M Tris buffer (pH 8.5). Electron microscopy revealed that the virions were dissociated to individual capsomers after a 15-min exposure. Addition of 5-20 millim Ca^{2+} to the reaction mixture completely prevented dissociation, whereas Mg^{2+} did not. Thus, Ca^{2+} has an important role in virion stability. X-ray fluorometry, inhibition studies, and incorporation of ^{45}Ca into complete and incomplete particles substantiate the presence of this cation in association with the virion. CsCl density gradient centrifugation indicated that both EGTA and DTT were necessary for dissociation to occur. Three protein species, 5S, 12S, and 18S, were observed by velocity sedimentation in sucrose gradients. The potential involvement of Ca^{2+} in other papovaviruses is discussed. (22 refs.)

- 77-6382 Identification of the Human Papovavirus T Antigen and Comparison with the Simian Virus 40 Protein A.** (Eng) Rundell, K. (Dept. Microbiology-Immunology, Northwestern Univ.-McGaw Medical Center, Chicago, IL 60611); Tegtmeyer, P.; Wright, P. J.; Di Mayorca, G. *Virology* 82(1): 206-213; 1977.

The structure of the T antigens produced by BKV-type human papovaviruses was compared with that of the simian virus 40 (SV40) A protein (T antigen) by immunoprecipitation and peptide mapping techniques. Cells infected with the BKV papovaviruses synthesized phosphoproteins that cross-reacted with antiserum directed against the SV40 A protein. These proteins could not be distinguished from the SV40 A protein by gel electrophoresis. Peptide map analyses indicate that the human virus proteins and SV40 proteins are similar, but not identical. At least two unique peptides are found in the maps of the human virus proteins, but a predominant peptide of the SV40 protein is missing. Structural analyses provide a direct procedure for detecting the presence and expression of viral genomes in host cells. (31 refs.)

- 77-6383 Absence of Papovavirus T Antibody in Patients with Malignancies (Letter to Editor).** (Eng.) Costa, J. (Lab. Pathology, Div. Cancer Biology and Diagnosis, NCI, Bethesda, MD 20014); Yee, C.; Rabson, A. S. *Lancet* 2(8040): 709; 1977.

Sera from 25 healthy controls and 88 cancer patients were tested for reactions against a battery of virally transformed cell lines. The studies failed to detect significant antibody titers to BK and JC virus T antigens. These findings suggest a lack of widespread association between these papovaviruses and human neoplasia. (2 refs.)

- 77-6384 Detection of Papova Virus in a Vaginal Aspirate (Letter to Editor).** (Eng.) Wachtel, E. (Univ. London, Inst. Obstetrics and Gynaecology, Hammersmith Hosp., Du Cane Road, London, W12 0HS, England). *Acta Cytol (Baltimore)* 21(4): 489-490; 1977.

A vaginal aspirate demonstrated the presence of Papova virus infection in a 58-yr-old woman. Cytological studies failed to demonstrate any abnormalities. Criteria for the recognition of these viruses in urine sediments are outlined. (no refs.)

- 77-6385 Polyoma Virus in Urine During Pregnancy (Letter to Editor).** (Eng.) Coleman, D. V. (Dept. Experimental Pathology, St. Mary's Hosp. Medical Sch., London W2 1NY, England); Daniel, R. A.; Gardner, S. D.; Field, A. M.; Gibson, P. E. *Lancet* 2(8040): 709-710; 1977.

Electron microscopy of the urine of a 38-yr-old woman in her 36th and 39th wk of pregnancy revealed the presence of JC polyomavirus. Serum BK antibody and JC hemagglutination-inhibition antibody were present both in the mother and in her child. A polyomavirus from another pregnant woman has since been cultured, and papovavirus particles have been observed in urine specimens from three others. (no refs.)

- 77-6386 Analysis of the Structure of Human Papilloma Virus DNA: Brief Report.** (Eng) DeLap, R. (Dept. Biochemistry, New York Univ. Sch. Medicine, 55 First Ave., New York, NY 10016); Yanagi, K.; Rush, M. C. *Arch Virol* 54(3): 263-269; 1977.

The DNA of human papilloma virus was examined for possible heterogeneity by electron microscopy, reassociation kinetics, and restriction endonuclease digestion. No heterogeneity in contour length was detected. Reassociation kinetics of papilloma DNA preparations isolated from pooled common warts indicated that it was essentially a single nonredundant DNA species, but the technique would not detect sequence redundancy or heterogeneity of 10%. Analyses of *EcoRI* restriction endonuclease digestion of 5 different papilloma DNA preparations each isolated from 20 pooled human warts, revealed minor fragments of atypical size in 3/5 preparations. *Hind III* digestion produced a single atypical DNA fragment in 4/5 of these same preparations. These results suggest the existence of minor strains of papilloma virus that are transmissible and can self-replicate, although these variants may be noninfectious byproducts of infections initiated by normal virions. (21 refs.)

- 77-6387 Early Lesions and Development of Primary Hepatocellular Carcinoma in Man--Association with Hepatitis B Viral Infection.** (Eng.) Okita, K. (First Dept. Internal Medicine, Yamaguchi Univ. Sch. Medicine, Ube City, Yamaguchi Prefecture, 755 Japan); Kodama, T.; Harada, T.; Noda, K.; Fukumoto, Y.; Takenami, T.; Shige, K.; Mizuta, M.; Takemoto, T. *Gastroenterol Jpn* 12(2): 51-54; 1977.

Studies were conducted to identify the premalignant lesions in chronic liver disease (CLD) that develops into primary hepatocellular carcinoma and to determine if there is an association between this premalignant lesion and hepatitis B virus (HBV) infection. Sera and biopsy specimens from more than 100 patients with CLD were examined. Fourteen of 14 cases with chronic active hepatitis showed liver cell dysplasia and 71.4% of these 14 cases also had > 200 nanograms α -fetoprotein (AFP) per milliliter of serum. In 13/55 cases with liver cirrhosis, serum AFP levels were even higher. The direct fluorescence antibody technique using rabbit anti-human ATP was performed in 20 patients with the high

vels of serum ATP; localization of ATP was seen in the
spastic cells. HBV-associated DNA polymerase activity
is also significantly high in the sera from patients with
chronic active hepatitis. This finding suggests a possible role
for HBV in the development of CLD, because HBV-
associated DNA polymerase may be used for HBV replica-
tion and for DNA synthesis in the host cells. The results also
indicate an association between AFP and liver cell dysplasia,
which is postulated as a precursor lesion of primary hepato-
cellular carcinoma. (36 refs.)

-6388 **Association of Human Hepatocellular Car-
cinoma and Cirrhosis with Hepatitis B Virus
Surface and Core Antigens in the Liver.** (Eng) Nayak, N. C.
(Dept. Pathology, All-India Inst. Medical Sciences, New Del-
hi 110016, India); Dhar, A.; Sachdeva, R.; Mittal, A.; Seth,
N.; Sudarsanam, D.; Reddy, B.; Waghlikar, U. L.; Red-
dy, C. R. *Int J Cancer* 20(5): 643-654; 1977.

Paraffin sections of livers from 50 cases of hepatocellular car-
cinoma (HCC), 58 cases of liver cirrhosis, and 54 cases of
other miscellaneous liver disorders (controls) were stained for
hepatitis B surface and core antigens (HBsAg and HBcAg)
by immunoperoxidase and immunofluorescence techniques.
HBsAg was detected in 94% of the HCC's, 71% of the cir-
rhotic livers, and only 2% of control livers; the corresponding
frequencies of HBcAg were 22%, 31%, and 0%. Peroxidase
staining detected smaller amounts of HBcAg than fluores-
cence, and it was also much more convenient for identifying
the antigen. Both antigens were present in 9/41 HCC cases,
13/39 cirrhosis cases and 0/25 controls. Most of these livers
contained 1+ HBsAg and 1+ to 2+ HBcAg, an antigen
expression pattern suggestive of a carrier state or, rarely, of
early chronic liver disease. Among all livers tested, HBsAg
alone was present in 48, both antigens in 21, and HBcAg
alone in none. HBsAg was seen inside tumor cells in four
cases, but no tumor showed HBcAg. Most HCC's were as-
sociated with cirrhosis (92%), and antigen-positive cirrhosis
had a higher chance of harboring HCC than antigen-negative
cirrhosis. HBsAg was detected in all four noncirrhotic livers
associated with HCC, and two of these also had HBcAg.
Antigen-positive cirrhosis was frequently associated with HBsAg.
These results are further evidence for a strong association of
hepatitis B virus with HCC. (46 refs.)

-6389 **Biochemical Study of KB-Cell Receptor for
Adenovirus.** (Eng) Hennache, B. (Unite Virolo-
gic Moleculaire no. 102 de l'INSERM, Place de Verdun,
59045 Lille Cedex, France); Boulanger, P. *Biochem J* 166(2):
217-247; 1977.

KB-cell plasma-membrane receptors for adenovirus were iso-
lated and partially characterized by three different ap-
proaches: affinity chromatography, immunoadsorption,

and cross-linking with a cleavable bifunctional reagent.
Affinity chromatography yielded six polypeptide
species of mol wts 78,000 (78K), 74K, 55K, 42K, 40K,
and 34K. The immunoadsorbent selected four major
protein subunits of 100K, 78K, 42K, and 34K mol wt.
The cross-linking procedure revealed three major poly-
peptide subunits of mol wts 78K, 60K, and 42K, along
with two discrete species of 88K and 34K. Thus, the
polypeptide species common to the three systems
were the 78K, 42K, and 34K subunits. The 42K and
34K polypeptides may be proteolytic fragments of higher mol
wt glycoproteins, such as the 78K species. Alternatively, the
42K subunit could correspond to actin subunits in the cell
membrane. The results suggest that there is a primary in-
teraction of the adenovirus fiber with the 78K glycoprotein
and that the 42K and 34K species are part of the primary
fiber-binding structure. (28 refs.)

77-6390 **Intracellular Forms of Adenovirus DNA. VI.
Quantitation and Characterization of the Four
Size-Classes of Adenovirus Type 2 DNA in Human KB Cells.**
(Eng.) Fanning, E. (Inst. Genetics, Univ. Cologne, Cologne,
W. Germany); Doerfler, W. *Virology* 81(2): 433-448; 1977.

In human KB cells productively infected with adenovirus
type 2 (Ad2), four size classes of viral DNA have been iden-
tified, quantitated, and partially characterized. The > 100S
and 50S-90S DNA classes represent viral DNA covalently
linked to cellular DNA. Approx 1,000-3,000 Ad2 DNA
genome equivalents are represented in these high-mol-wt
forms of viral DNA. They may be parental viral DNA's that
are integrated into the cellular genome early in the course of
infection. Most of the newly synthesized viral DNA is found
in the 34S class, a size that represents the unit-genome length
of Ad2 DNA. Under optimal conditions, > 460,000 viral
DNA copies/cell are produced. A < 20S DNA class con-
tains fragments of viral DNA. Analysis of the various size
classes of DNA by reassociation kinetics with restriction
fragments of Ad2 DNA revealed that all parts of the viral
DNA are about equally represented in the 34S DNA. The
50S-90S DNA contains the right molecular end in a 10- to
15-fold excess over the left terminus, and the < 20S DNA
contains the right-end sequences in a 2- to 4-fold excess. In
the > 100S DNA, the left end of the Ad2 DNA is in excess.
Several possible explanations, including preferential replica-
tion and integration, for the unequal representation of the
Ad2 DNA sequences in the different size classes are given.
(47 refs.)

77-6391 **Nuclear Matrix of HeLa S₂ Cells: Polypeptide
Composition During Adenovirus Infection and
in Phases of the Cell Cycle.** (Eng) Hodge, L. D. (Dept. Hu-
man Genetics, Yale Univ. Sch. Medicine, New Haven, CT

06510); Mancini, P.; Davis, F. M.; Heywood, P. *J Cell Biol* 72(1): 194-208; 1977.

A nuclear fraction was isolated from uninfected and adenovirus 2-infected HeLa S₃ nuclei after treatment with high salt buffer, deoxyribonuclease, and dithiothreitol, and its ultrastructural and biochemical properties were examined. This fraction, which retained the approx size and shape of the nuclei, consisted of nonmembranous and membranous elements. Chemically, it was 87% protein, 12% phospholipid, 1% DNA, and 0.1% RNA by wt. The protein constituents were resolved in sodium dodecyl sulfate polyacrylamide slab gels into 30-35 distinguishable bands in the mol wt range 14,000 (14K)-200K, with major peptides at 14K-18K and 45K-75K. Analysis of newly synthesized polypeptides by cylindrical gel electrophoresis revealed another cluster in the 90K-130K range. Twenty-two hours after adenovirus infection, the amounts of the three major polypeptides in the 45K-75K range were reduced. Concomitantly, three new polypeptides appeared that migrated as the virus-coded proteins, major core protein VII at 21K, p-VII precursor to the major core at 23K, and 100K at 92K mol wt. It is suggested that the small amount of residual DNA in the matrix represents initiation sites for replication. Furthermore, p-VII, which is present in the nuclear matrix in greater relative abundance (compared to VII) than it is in the nucleoplasm or cytoplasm, may be involved in a fixing-point for the initiation of viral assembly. (44 refs.)

77-6392 An Amazing Sequence Arrangement of the 5' Ends of Adenovirus 2 Messenger RNA. (Eng) Chow, L. T. (Cold Spring Harbor Lab., Cold Spring Harbor, NY 11724); Gelinas, R. E.; Broker, T. R.; Roberts, R. J. *Cell* 12(1): 1-8; 1977.

The 5' terminal sequences of several adenovirus 2 (Ad2) messenger RNA's (mRNA's), isolated late in infection, are complementary to sequences with the Ad2 genome that are remote from the DNA from which the main coding sequence of each mRNA is transcribed. This was observed by forming RNA displacement loops (R loops) between AD2 DNA and unfractionated polysomal RNA from infected cells. The 5'-terminal sequences of mRNA's in R loops, variously located between positions 36 and 92, formed complex secondary hybrids with single-stranded DNA from restriction endonuclease fragments containing sequences to the left of position 36 on the Ad2 genome. The structures visualized in the electron microscope showed that short sequences coded at map positions 16.6, 19.6, and 26.6 on the R strand are joined to form a leader sequence of 150-200 nucleotides at the 5' end of many late mRNA's. A late mRNA that maps to the left of position 16.6 shows a different pattern of second site hybridization. It contains sequences from 4.9 to 6.0 linked directly to those from 9.6 to 10.9. These findings imply a new mechanism for the biosynthesis of Ad2 mRNA in mammalian cells. (34 refs.)

77-6393 Reassociation of Complementary Strand-specific Adenovirus Type 2 DNA with Viral DNA Sequences of Transformed Cells. (Eng.) Johansson, K. (Dept. Microbiology, Biomedical Center, Univ. Uppsala, Uppsala, Sweden); Pettersson, U.; Philipson, L.; Tibbetts, C. *J Virol* 23(1): 29-35; 1977.

³²P-labeled, complementary strand-specific sequences of adenovirus type 2 (Ad2) DNA, representing the entire viral genome or selected restriction fragments, were used as probes in DNA reassociation experiments to characterize viral sequences in two Ad2-transformed rat cell lines, A₂F₁₉ and A₂T₂C₄. Viral probe DNA and cellular DNA samples were degraded to about 350 nucleotides and incubated to ensure exhaustive reassociation. Viral DNA sequences in A₂F₁₉ cells represented only 12%-14% of the Ad2 viral genome at a level of about seven copies per diploid equivalent. Using the entire Ad2 strand as a probe, A₂T₂C₄ cells contained about 56% of the Ad2 genome at two to three copies per diploid equivalent. Sequences corresponding to all four *Bam*HI fragment probes were observed with about one to five copies per diploid equivalent. The results demonstrate the advantages of using strand-specific probe DNA to estimate the number of copies of viral sequences per cell and the fraction of the viral genome represented by these sequences. (22 refs.)

77-6394 Adenovirus DNA-binding Protein in Cells Infected with Wild-Type 5 Adenovirus and Two DNA-minus, Temperature-sensitive Mutants, H5ts125 and H5ts149. (Eng.) Ginsberg, H. S. (Dept. Microbiology, College of Physicians and Surgeons, Columbia Univ., New York, NY 10032); Lundholm, U.; Linne, T. *J Virol* 23(1): 142-151; 1977.

KB cells were infected with 0.1-0.5 plaque-forming unit of wild-type adenovirus type 5, or either of two DNA-minus, temperature-sensitive mutants, H5ts125 and H5ts149. The cells were then incubated at 32 C for 24 hr, labeled with ³⁵S-methionine for 30 min, cultured at 32 C for an additional 30 min, and shifted to 39.5 C (nonpermissive temperature of H5ts125). Analysis by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and autoradiography showed a significant decrease in the 72,000 (72K)-mol wt DNA-binding protein in H5ts125-infected cells. In contrast, the 72K protein was stable in cells infected by H5ts149 and wild-type at 39.5 C. Immunofluorescent tests indicated that immunologically reactive DNA-binding protein almost disappeared after 6 hr at 39.5 C in H5ts125-infected cells. A return to 32 C caused the reactive protein to reappear, even in the presence of 10 µg of cycloheximide, an inhibitor of protein synthesis. The data indicate that the single-strand-specific DNA-binding protein is essential for initiation of viral synthesis but not for elongation of viral DNA strands. (20 refs.)

- 6395 **Transformation of a Rat Cell Line by an Adenovirus Type 12 DNA Fragment.** (Eng) Sano, S. (Cancer Res. Inst., Sapporo Medical Coll., Sapporo, Japan); Ojima, S.; Fujinaga, K.; Shiroki, K.; Shimojo, H. *Virology* 82(1): 214-220; 1977.

The transforming segment of human adenovirus 12 (Ad 12) was investigated using a rat clonal cell line, 3Y1, established from a Fischer rat embryo in vitro. The results indicate that the *Eco*RI-C fragment of Ad12 DNA, as well as whole Ad12 DNA, was capable of transforming the 3Y1 cells and that the transformed cells contained Ad12-specific T antigen. Furthermore, WY3, the cell line transformed by whole Ad12 DNA, and CY1, the cell line transformed by the *Eco*RI-C fragment of Ad12 DNA, contained the Ad12 DNA sequences and sequences of at least part of the *Eco*RI-C fragment, respectively. This model system may be useful in investigating the mechanism of viral carcinogenesis. (22 refs.)

- 6396 **Helper Factor(s) for Growth of Adeno-associated Virus in Cells Transformed by Adenovirus 12.** (Eng) Handa, H. (Inst. Medical Science, Univ. Tokyo, 4-6-1, Shirokanedai, Minato-ku, Tokyo 108, Japan); Shiroki, K.; Shimojo, H. *Proc Natl Acad Sci USA* 74(10): 4508-4510; 1977.

The helper factor(s) for the growth of adeno-associated virus (AAV) was demonstrated to be present in cells transformed by adenovirus type 12 (Ad12). The growth of AAV was observed in heterokaryons formed by fusion of human KB and Ad12-transformed Fischer rat embryo cells using UV-inactivated Sendai virus without coinfection of cells with adenovirus. The presence of the helper factor(s) for AAV growth in rat cells transformed by the *Eco*RI-C fragment of the *Hind*III-G fragment of Ad12 DNA suggests that the helper factor(s) induced by infection with adenovirus is the Ad12-specific T antigen. (17 refs.)

- 6397 **Detection of Herpes Simplex Virus-related Antigens in the Nuclei and Cytoplasm of Biochemically Transformed Cells with Peroxidase/Anti-peroxidase Immunological Staining and Indirect Immunofluorescence.** (Eng) Kurchak, M. (Div. Biochemical Virology, Baylor College of Medicine, Houston, TX 77030); Dubbs, D. R.; Kit, S. *J Cancer* 20(3): 371-380; 1977.

Herpes simplex virus (HSV)-related antigens were detected in the nuclei and cytoplasm of human [HeLa(BU25)] and mouse [LM(TK-)] cells biochemically transformed by UV-irradiated HSV. Detection was accomplished by peroxidase/antiperoxidase immunological staining and indirect immunofluorescence with rabbit antisera that had high neutralizing titers against HSV-specific thymidine kinase (TK) activity and virus infectivity. A positive reaction was seen

when HSV-1 antisera were tested against cells biochemically transformed by HSV type 1 (HSV-1), but not when HSV-1 antisera were tested against cells biochemically transformed by HSV-2. Similarly, a positive reaction was seen with HSV-2 antisera and HSV-2-transformed cells, but not HSV-1-transformed cells. In contrast, when cells were cytologically infected with HSV-1 or HSV-2, they reacted positively when treated with both HSV-1 and HSV-2 antisera. These findings suggest that biochemically transformed cells produce a type-specific subset of viral antigen (including, eg, TK), while cells productively infected produce a wider range of HSV antigens. (21 refs.)

- 77-6398 **Quantification of the Herpes Simplex Virus DNA Present in Biochemically Transformed Mouse Cells and Their Revertants.** (Eng.) Sugino, W. M. (Dept. Medical Microbiology, Sch. Medicine, Univ. California, Irvine, CA 92717); Chadha, K. C.; Kingsbury, D. T. *J Gen Virol* 36(1): 111-122; 1977.

The herpes simplex virus (HSV) DNA in biochemically transformed mouse cells and revertant clones was studied using DNA hybridization and reassociation techniques. Four cell lines biochemically transformed by UV-irradiated HSV contained virus DNA fragments ranging from 3% to 22% of the HSV genome. Of five revertant clones selected for ³H-thymidine or bromodeoxyuridine (BUdR) resistance, four had lost all detectable virus DNA while the fifth, selected for BUdR resistance, retained the entire virus fragment but showed a reduction of virus copies per cell of from five to one. Three super-transformed (biochemically transformed cells derived from revertants of previously transformed clones) revertant cell lines contained virus DNA fragments ranging from 12% to 28%. The number of virus DNA fragments per cell ranged from one to five and indicated that a single copy of the virus thymidine kinase gene is adequate for biochemical transformation. Determination of the base composition of the transforming virus DNA fragment indicated that the transforming DNA has a base composition approx the same as the HSV genome and does not constitute a low GC virus DNA region. Cross hybridization between HSV-1-transformed cells and HSV-2 DNA was very slight, indicating that the DNA found in the clone that retained the entire virus fragment was not entirely composed of the HSV-1 and HSV-2 common sequences. These studies suggest that the max required fragment of HSV DNA for the biochemical or morphological transformation of cells is 3%-4% of the virus genome. The results also suggest that obtaining the required transforming genes in pure form and using that DNA as a hybridization probe may be the only reliable assay for the HSV DNA in transformed cells and human tumors. (12 refs.)

- 77-6399 **Effects of Herpes Simplex Virus on Sister Chromatid Exchange and Chromosome Abnor-**

malities in Human Diploid Fibroblasts. (Eng) Kato, H. (Roswell Park Memorial Inst., New York Dept. Health, Buffalo, NY 14263); Sandberg, A. A. *Exp Cell Res* 109(2): 423-427; 1977.

To study viral effects on sister chromatid exchange (SCE), human diploid fibroblasts were infected with herpes simplex virus types 1 and 2. The viruses produced remarkable chromosome aberrations in the early phases of the infection, but neither caused an increase in the SCE frequency over the uninfected control level. Analysis of the breakpoints of chromatid deletions with respect to their association with SCE revealed that the virus-induced chromatid deletions arose independently of the SCE sites. It is probable that the genesis of virus-induced chromosome aberrations is unrelated to the molecular processes that function in SCE formation. (19 refs.)

77-6400 Quantitative Study of Alterations in the Nuclei of Human Hepatocytes Induced by Herpes Virus (HSV₂) (Meeting Abstract). (Fre) Scotto, J. (Unité d'Hépatologie Infantile-U56, INSERM, 94270 Kremlin-Bicêtre, France); Sauron, B.; Dupuy-Coin, A. M. *Biol Cellulaire* 29(1): 41a; 1977. (no refs.)

77-6401 ELISA for Herpes Simplex Virus Type 2 Antibodies (Letter to Editor). (Eng) Grauballe, P. C. (Inst. Medical Microbiology, Univ. Copenhagen, DK-2100 Copenhagen, Denmark); Vestergaard, B. F. *Lancet* 2(8046): 1038-1039; 1977.

A test for the titration of herpes simplex virus (HSV) type 2 specific antibodies in human sera uses an enzyme-linked immunosorbent assay (ELISA) with HSV type 2 specific antigens obtained by immunoabsorption. This assay will facilitate epidemiologic studies on the role of HSV type 2 in carcinoma of the uterine cervix. (7 refs.)

77-6402 Chromosomal Site(s) of Integration of Herpes Simplex Virus Type 2 Thymidine Kinase Gene in Biochemically Transformed Human Cells. (Eng) Donner, L. (Div. Biochemical Virology, Baylor Coll. Medicine, Houston, TX 77030); Dubbs, D. R.; Kit, S. *Int J Cancer* 20(2): 256-267; 1977.

Experimental evidence is presented which indicates that herpes simplex virus type 2 (HSV-2) thymidine kinase (TK) activity is expressed in seven lines of human-mouse somatic cell hybrids CHL/1-HL/7, consisting of HeLa cells fused with TK-deficient mouse fibroblasts [LM(TK-)]. Furthermore, all hybrid cell lines and subclones tested contained one or more human chromosomes. After counter-

selection in bromodeoxyuridine (BUdR) medium, BUdR-resistant subclones resulted that had lost both the TK activity and human chromosomes. The presence of the M13 chromosome (isochromosome of the short arm of human chromosome X) in most of the cells in 6/7 somatic hybrids and the loss of this chromosome in all cells of BUdR-counterselected, HSV-2 TK-negative subclones implies that the HSV-2 TK gene was integrated in this chromosome. (33 refs.)

77-6403 Epstein-Barr Virus and Nasopharyngeal Carcinoma: Is There an Etiologic Relationship? (Eng) Henderson, B. E. (Dept. Pathology, Univ. Southern California Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA 90033); Louie, E. W.; Jing, J. S.; Alena, B. *J Natl Cancer Inst* 59(5): 1393-1395; 1977.

The serologic association between Epstein-Barr virus (EBV) and nasopharyngeal carcinoma (NPC) was reexamined to determine whether the association indicates an etiologic role for EBV or whether the virus is "passenger" in the neoplastic tissue. Antibody titers to all the EBV-related antigens were significantly ($p < 0.001$) elevated in NPC patients compared with controls. The EBV antibody titers for early antigen (EA) and anti-diffuse titers of Chinese-American and black patients with NPC were significantly higher than those of white patients with NPC. Virus capsid antigen (EB-VCA) antibody titers were higher in the Chinese-American and black patients, but the anti-restricted (R) component was higher in the white patient group. However, these differences were not statistically significant. The EB-VCA antibody titers were elevated in all white patients with squamous cell carcinoma of the pharynx, regardless of the subsite involved. The geometric mean titers to VCA, EA and the anti-R component in NPC and oropharyngeal carcinoma was significantly elevated ($p < 0.05$) above those of controls. These results are discussed in relation to the role of EBV as an etiologic cofactor or as a passenger in neoplastic tissue. (20 refs.)

77-6404 Relationship Between the Epstein-Barr Virus and Undifferentiated Nasopharyngeal Carcinoma: Correlated Nucleic Acid Hybridization and Histopathological Examination. (Eng) Andersson-Anvret, M. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Forsby, N.; Klein, G.; Henle, W. *Int J Cancer* 20(4): 486-494; 1977.

To evaluate the association between Epstein-Barr virus (EBV) DNA and nasopharyngeal carcinoma (NPC), a correlated histopathologic and nucleic acid hybridization study was performed on 51 undifferentiated NPC, 4 NPC with some signs of squamous differentiation, 7 nasopharyngeal tumors of other histologic types, and 14 head and neck car-

nomas located outside the nasopharynx. All 51 undifferentiated NPC's contained significant numbers of EBV-genome copies per cell. Two of the NPC's with squamous differentiation were also EBV-DNA positive. Of the other nasopharyngeal tumors, 1/7 was EBV-DNA-positive. Histological examination, however, showed that this was a typical Burkitt's lymphoma. The other six tumors were all EBV-DNA-negative lymphoproliferative malignancies. All 14 head and neck carcinomas located outside the nasopharynx were EBV-DNA-negative. The sera of undifferentiated NPC patients had elevated antibody titers against the EBV-determined antigens, particularly the early antigen (diffuse) component. These findings confirm that there is a regular association between EBV-DNA and undifferentiated NPC. (29 refs.)

6405 **Clonal Transformation of Adult Human Leukocytes by Epstein-Barr Virus.** (Eng) Sugden, (McArdle Labs., Univ. Wisconsin, Madison, WI 53706); Mark, W. *J Virol* 23(3): 503-508; 1977.

Adult human mononuclear WBC isolated from four Epstein-Barr virus (EBV)-seronegative donors were infected with dilutions of EBV suspended in a second layer of agarose over human fibroblast (10^5 cells/15-mm well) feeder layer covered with agarose. Progeny of the clones were subsequently assayed on γ -irradiated fibroblast feeder layers. EBV transformation occurred in a dose-dependent manner. Freshly transformed clones harbored viral DNA with a sequence complexity similar to that of DNA in virus stocks. The cloning efficiency of newly transformed colonies was about 3% and independent of the number of transformed cells seeded. About 1/30 to 1/50 of the adult WBC appeared capable of being transformed. When human WBC were infected with excess of EBV, between 1/1,000 and 1/5,000 cells formed a colony of transformed cells. At least between 1/30 and 1/100 DNA-containing EBV particles from the virus stock were infectious. Assay permits analysis of the numerical balance between viral and host genomes and monitoring clonal variations. (16 refs.)

6406 **Comparative Studies on Adult Donor Lymphocytes Infected by EB Virus In Vivo or In Vitro: Origin of Transformed Cells Arising in Co-cultures with Fetal Lymphocytes.** (Eng.) Rickinson, A. B. (Dept. Pathology, Univ. Bristol Medical Sch., Univ. Walk, Bristol BS8 1TD, England); Finerty, S.; Epstein, M. A. *Int J Cancer* 21(6): 775-782; 1977.

Cultures were set up that contained equal numbers of mononuclear cells from the blood of Epstein-Barr virus (EBV)-infected individuals, either acute infectious mononucleosis (IM) patients (2×10^6 cells) or healthy seropositive (SP) adult donors (10^7 cells), and fetal cord

blood mononuclear cells of the opposite sex. Transformed cells arising in the cocultures were subcultured, and their cellular origin was determined by chromosome analysis. When cells were exposed to EBV at the beginning of the culture period, transformed foci of mixed cellular origin developed within 2-3 wk, with fetal cells often in the majority. In experiments without EBV exposure, IM/fetal cultures showed transformation after 4-5 wk with fetal cells also predominant, but SP/fetal cultures showed a low incidence of transformation. When mononuclear cells from a seronegative donor (2×10^3 - 10^5 cells) were exposed to EBV and cocultured 5-12 days later with an excess (2×10^6 cells) of fetal mononuclear cells of the opposite sex, transformed foci were predominantly of adult donor origin. These results support the concept of a two-step mechanism involving virus release and secondary infection of cocultured cells. (30 refs.)

77-6407 **Epstein-Barr Virus: Transformation of Lymphocytes Separated by Size or Exposed to Bromodeoxyuridine and Light.** (Eng) Henderson, E. (Dept. Pediatrics, Yale Univ. Sch. Medicine, New Haven, CT 06510); Robinson, J.; Frank, A.; Miller, G. *Virology* 82(1): 196-205; 1977.

Several experimental approaches were used to compare the efficiency of Epstein-Barr virus (EBV) transformation and viral-induced stimulation of DNA synthesis in lymphocyte populations that varied in their degree of activation. No correlation was found between DNA synthesis and susceptibility to EBV transformation. A subpopulation of human cord blood lymphocytes that are susceptible to EBV transformation were not actively synthesizing DNA at the time of viral exposure. After removal of the larger DNA-synthesizing lymphocytes, there remained a partially purified homogenous population of B lymphocytes in a resting state that were highly susceptible to transformation. Furthermore, pretreatment of cultured human umbilical cord blood cells and marmoset cells with bromodeoxyuridine ($50 \mu\text{g/ml}$ culture) for 24 hr and then to visible light, before and at various times after virus exposure, reduced spontaneous DNA synthesis markedly, but susceptibility to transformation was not altered. On the basis of these data, it is hypothesized that transformation of resting lymphocytes by EBV occurs when the virus per se stimulates DNA synthesis de novo in the infected cell or that virus-infected cells may undergo spontaneous DNA synthesis after virus exposure and may then be transformed. (21 refs.)

77-6408 **Further Studies on the Differences in Serum Dependence in EBA Negative Lymphoma Lines and Their In Vitro EBV Converted, Virus-Genome Carrying**

Sublines. (Eng) Steinitz, M. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Klein, G. *Eur J Cancer* 13(11): 1269-1275; 1977.

Independently Epstein-Barr virus (EBV)-converted, viral genome-carrying sublines of the originally EBV-negative Ramos and BJAB lymphoma lines showed decreased serum dependence, in comparison with progenitor lines. The virus-negative lines could not grow in 10% dialyzed fetal calf serum unless it was reconstituted with the dialyzate. The converted lines grew well on dialyzed serum. Seeding of the EBV-negative lines with larger inocula enabled them to grow on dialyzed serum as well. In contrast to the original negative lines, the EBV-converted lines were able to form colonies in soft agar. (16 refs.)

77-6409 Radioimmunoassay for Epstein-Barr Virus (EBV)-associated Nuclear Antigen (EBNA). Binding of Iodinated Antibodies to Antigen Immobilized in Polyacrylamide Gel. (Eng) Dolken, G. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Klein, G. *Eur J Cancer* 13(11): 1277-1286; 1977.

A solid-phase radioimmunoassay was developed for Epstein-Barr virus (EBV)-associated nuclear antigen (EBNA). Total homogenates of EBV-DNA- and EBNA-positive or -negative cells were polymerized in polyacrylamide gel and compared for their ability to bind ^{125}I -IgG prepared from anti-EBNA-positive and anti-EBNA-negative sera. EBNA specific binding was demonstrated and confirmed by serological and cellular specificity controls. The assay permits the quantitation of antigen or antibody even in the presence of detergents, and it is suitable for biochemical characterization of the antigen. Reciprocal blocking studies with extracts from different cell lines showed quantitative and qualitative differences. One part of the EBNA specificities present in the human Burkitt's lymphoma-derived lines RAJI, DAUDI, and AW-RAMOS was missing in B95-8, a marmoset line carrying EBV derived from a human infectious mononucleosis line. This result may reflect differences in the viral genomes derived from Burkitt's lymphoma and infectious mononucleosis lines or differences in the host cells. (35 refs.)

77-6410 Solubilization of Epstein-Barr Virus (EBV)-associated Nuclear Antigen from Raji Cells and Chromatin by Treatment with Various Molarities of NaCl. (Eng.) Brown, T. D. (Beatson Inst. Cancer Res., Wolfson Lab. Molecular Pathology, Gartcube Estate, Switchback Road, Bearsden, Glasgow, Scotland); Rickwood, D.; MacGillivray, A. J.; Klein, G. *Cancer Lett* 3(3-4): 151-156; 1977.

The solubilization of Epstein-Barr virus-associated nuclear antigen (EBNA) by various molarities of NaCl was studied by ^{125}I -IgG absorption assay. Very little antigenic activity (<

10%) was solubilized in 0.15 M NaCl sonic extracts of Raji cells, but 2.0 M NaCl could solubilize much of the activity. However, when the 2.0 M NaCl was dialyzed back to 0.15 M NaCl, most of the EBNA was found in the pellet. Examination of Raji chromatin revealed that 0.14 M NaCl solubilized little of the EBNA and that 0.35 M NaCl extracted more EBNA, but a considerable amount still remained bound to the chromatin. The extraction efficiency is increased if the chromatin is treated with 2.0 M NaCl followed by dialysis to 0.35 M NaCl. These results suggest that EBNA may be a tightly bound chromatin-associated nonhistone protein. (16 refs.)

77-6411 Identification of a Purified Complement-fixing Antigen as the Epstein-Barr-Virus-determined Nuclear Antigen (EBNA) by Its Binding to Metaphase Chromosomes. (Eng.) Ohno, S. (Dept. Tumor Biology and Chemistry, Karolinska Inst., 104 01 Stockholm 60, Sweden); Luka, J.; Lindahl, T.; Klein, G. *Proc Natl Acad Sci USA* 74(4): 1605-1609; 1977.

When 100 μl (1.0-1.2 μg of protein) of purified complement-fixing (CF) antigen from the Burkitt's lymphoma-derived cell line Raji was added to smears of methanol/acetic acid-fixed Raji metaphase chromosomes, brilliant positive fluorescence was observed by anticomplement immunofluorescence with sera containing anti-EBNA (Epstein Barr virus-determined nuclear antigen) antibodies. EBNA-negative controls gave no staining. These data show that it is possible to reconstitute acid-treated Raji chromosomes with purified CF antigen to elicit a staining equivalent to the original EBNA staining. Results of experiments with Ramos (human lymphoma, EBNA-negative) cells indicate that purified CF antigen can bind to EBNA-negative chromosomes and convert them to a positive state. Purified CF antigen cochromatographed with EBNA on Sephadex G-200. The soluble, purified antigen identified as EBNA was estimated to have a mol wt of $174,000 \pm 15,000$ daltons, as determined by gel filtration and sucrose gradient centrifugation. (30 refs.)

77-6412 Analysis of the Factors of Tumorigenesis in Humans, Using Epstein-Barr Virus as an Example. (Ger.) Henle, W. (Div. Virology, Children's Hosp. Philadelphia, Philadelphia, PA). *Naturwiss Rundsch* 30(4): 132-133; 1977.

The immunologic relationship between Burkitt's lymphoma, nasopharyngeal carcinoma, and Epstein-Barr virus (EBV) has been shown by the presence of EBV DNA in 100% of the biopsies of the two neoplasms and the transformation of normal lymphocytes by EBV into lymphoblastlike cells that are indistinguishable from Burkitt's lymphoma cells. (no refs.)

77-6413 **Biologic and Antigenic Characteristics of Epstein-Barr Virus-related Herpesviruses of Chimpanzees and Baboons.** (Eng.) Gerber, P. (Dept. Health, Education and Welfare, Food and Drug Admin., Bureau Biologies, Div. Virology, Bethesda, MD 20014); Kalter, S. S.; Schidlovsky, G.; Peterson, W. D.; Daniel, M. D. *Int J Cancer* 20(3): 448-459; 1977.

Epstein-Barr virus (EBV)-related herpesviruses (HV) of chimpanzees and baboons were identified and partially characterized. Baboon lymphoid cells were transformed by agents isolated from the oral secretions of 2/3 chimpanzees that had been immunosuppressed with anti-human thymocyte serum globulin. Approx 5%-10% of these cells contained cytoplasmic antigens reactive with EBV-antibody-positive (VCA+) chimpanzee, human, and baboon sera, and they produced infectious virus. In addition, WBC from 5/9 EBV-seropositive baboons underwent spontaneous transformation after 24-45 days in culture; in each of these five cell lines, 5%-10% of the cells were VCA+. The transformed lymphoblasts had B-cell surface markers. Electron microscopy of the transformed cells revealed the presence of herpesvirus particles. Both the baboon and chimpanzee HV's were able to transform lymphocytes from human newborns and from several species of nonhuman primates. When the baboon and chimpanzee HV's were injected into baboons, rhesus monkeys, or marmosets, seroconversion occurred, but no illness or palpable tumor ensued. Immunologic cross-neutralization studies revealed the relatedness of the baboon and chimpanzee HV's with EBV. (35 refs.)

77-6414 **Establishment of a Cell Line with Associated Epstein-Barr-like Virus from a Leukemic Orangutan.** (Eng.) Rasheed, S. (Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles CA 90033); Rongey, R. W.; Bruszewski, J.; Nelson-Rees, W. A.; Rabin, H.; Neubauer, R. H.; Esra, G.; Gardner, M. B. *Science* 198(4315): 407-409; 1977.

A herpesvirus similar to Epstein-Barr virus was isolated from a lymphoid cell line derived from an orangutan (*Pongo pygmaeus*) with subacute myelomonocytic leukemia. Intranuclear and intracytoplasmic herpesvirus particles were seen by electron microscopy. Karyotype analyses of blood cells and skin fibroblasts revealed abnormalities (deletions of chromosomes No. 22 and X and monosomy of Nos. 12 and 17) distinct from those usually observed in human leukemia. (23 refs.)

77-6415 **Simian Virus 40-Chinese Hamster Kidney Cell Interaction. IV. Enhanced Virus Replication in Infected Cells upon Treatment with Mitomycin C.** (Eng.) Lalle, C. (Institut de Recherches Scientifiques sur le Cancer, B.P. N8, 94800 Villejuif, France); Morris, A. G.; Suarez, H.

G.; Estrade, S.; Stevenet, J.; Cassingena, R. *J Gen Virol* 36(1): 137-149; 1977.

The effect of mitomycin C (MM-C) on simian virus 40 (SV40) replication in infected Chinese hamster kidney cells was studied. Upon infection with SV40 or SV40 DNA, Chinese hamster kidney cells supported virus DNA and virus synthesis at a low level. Treatment of these cells with MM-C 2 hr after infection with virus DNA significantly enhanced the yield of virus (10- to 100-fold). Max stimulation occurred upon a 3-hr exposure of the infected cells to 2 μ g/ml MM-C. MM-C treatment was equally efficient at increasing virus production whether carried out before or after infection. A simultaneous increase in the number of V antigen-synthesizing cells and virus-producing cells, as well as virus burst size, was observed following MM-C pretreatment, but the proportion of tumor antigen-synthesizing cells remained unchanged. MM-C pretreatment stimulated virus DNA replication in SV40-infected cells. Cells treated with MM-C exhibited an unbalanced growth pattern, with continuing protein synthesis in the absence of cell division and a markedly reduced ability to replicate cellular DNA. These results suggest that MM-C enhances the permissiveness of Chinese hamster kidney cells by inducing the synthesis of a specific cellular factor required for SV40 replication in these cells. Exposure to UV also enhanced infectious virus production, but exposure to caffeine inhibited it. (26 refs.)

77-6416 **Measurement of the Genome Sizes of Simian Virus 40 and Polyoma Virus.** (Eng.) Sompayrac, L. (Dept. Molecular, Cellular and Developmental Biology, Univ. Colorado, Boulder, CO 80309); Danna, K. J. *J Virol* 24(2): 695-700; 1977.

The genome sizes of Simian Virus (SV) 40 strain 776 and polyoma virus (Pasadena strain) were measured using the HindIII-D fragment as a standard. Since the HindIII-D fragment was determined to be 10.5% of the SV40 genome and 10.35% of the polyoma genome, the genomes of the respective virus strains must have $5,010 \pm 125$ base pairs and $5,080 \pm 125$ base pairs. (15 refs.)

77-6417 **Comparison of the Nucleotide Sequence of the Messenger RNA for the Major Structural Protein of SV40 with the DNA Sequence Encoding the Amino Acids of the Protein.** (Eng.) Celma, M. L. (Dept. Human Genetics, Yale Univ. Sch. Medicine, New Haven, CT 06510); Dhar, R.; Pan, J.; Weissman, S. M. *Nucleic Acids Res* 4(8): 2549-2559; 1977.

A comparison was made between the oligonucleotides in the simian virus 40 (SV40) 16S late messenger RNA directing the synthesis of the major viral structural protein (VP1) and those that would be present in a transcript of the portion of

SV40 DNA coding for VP1. A segment of about 200 nucleotides of RNA apparently transcribed from a distant part of SV40 DNA has become linked to the transcript of VP1 codons by a bond resistant to both phenol extraction and denaturation in formamide. (10 refs.)

- 77-6418 A Biochemical Method for Increasing the Size of Deletion Mutations in Simian Virus 40 DNA.** (Eng.) Shenk, T. (Dept. Microbiology, Univ. Connecticut Health Center, Farmington, CT 06032). *J Mol Biol* 113(3): 503-515; 1977.

A method has been developed for increasing the size of a deletion mutant in simian virus 40 (SV40) DNA. Closed-circular SV40 DNA from a deletion mutant (d1892), which lacks about 35 base-pairs at 0.675 to 0.68 SV40 map unit, and its wild-type parent were cleaved with *EcoRI* restriction endonuclease to generate full-length DNA's. The mutant and wild-type linear DNA's were mixed, denatured, and reannealed to form duplex structures that were recircularized by incubating with bacteriophage T4 DNA ligase. These closed-circular molecules, half of which contained a small deletion loop at 0.675 to 0.68 map unit, were treated with S1 endonuclease, which cleaved them at the site of the deletion loops to produce linear molecules with ends at 0.675 to 0.68 map unit. Mutants containing enlarged deletions were obtained by infecting permissive monkey kidney cells with the linear DNA. Two factors contribute to the enlargement process: (1) S1 endonuclease digests about 30 base-pairs from the ends of duplex DNA during cleavage, and (2) several base-pairs are lost from the ends of the DNA during cell-mediated closure of blunt-ended linear molecules to generate circular DNA. The mutants, all of which were viable, lacked 45 to 90 base-pairs, based on the altered migration of the *Hin c* II + *Hin d* III C fragments. The location of each enlarged deletion, determined by the S1 endonuclease mapping procedure, was compared to that of the parental mutant. One end of the parental deletion (at 0.675 map unit) remained essentially unmoved; the deletions were enlarged almost entirely in the opposite direction. This finding is consistent with the hypothesis that 0.675 map unit marks a boundary between a region of the genome known to contain nonessential sequences (0.675 to 0.74 map unit) and a portion required for lytic growth. (29 refs.)

- 77-6419 Infectious Linear DNA Sequences Replicating in Simian Virus 40-infected Cells.** (Eng) Gruss, P. (Institut für Virusforschung, Deutsches Krebsforschungszentrum, 69 Heidelberg, W. Germany); Sauer, G. *J Virol* 21(2): 565-578; 1977.

Small linear and nicked-circular DNA fragments were isolated from simian virus 40 (SV40)-infected CV-1 cells by selective extraction and banding in buoyant density equilibrium

gradients. These structures comprised up to 35% of the radioactively labeled DNA molecules that can be isolated by selective extraction. These molecules correspond to the length of an open SV40 DNA molecule (FO III), and they contain a heterogeneous population of DNA sequences of host or viral origin; some of these sequences have lost some of their endonuclease recognition sequences. Part of the FO III DNA molecules contain viral-host DNA sequences covalently linked with each other. Replication begins with the onset of SV40 superhelix replication 1 day after infection, and synthesis is most pronounced 3 days after infection when superhelix replication is declining. Some of these molecules prove infectious when administered to permissive cells. Following intracellular circularization, superhelical DNA FO I with an aberrant cleavage pattern accumulates; tumor and viral capsid antigen are induced and infectious viral progeny are obtained. Infection of cells with purified SV40 FO I DNA does not result in FO III DNA in the infected cells or in the viral progeny. These FO III DNA molecules could thus be perpetuated within SV40 pools by encapsidation into pseudovirions. (31 refs.)

- 77-6420 Characterization of the Autoregulation of Simian Virus 40 Gene A.** (Eng) Alwine, J. C. (Dept. Biochemistry, Stanford Univ. Sch. Medicine, Stanford, CA 94305); Reed, S. I.; Stark, G. R. *J Virol* 24(1): 22-27; 1977.

CV-1 cells infected by temperature-sensitive A (*tsA*) mutant of simian virus 40 (SV40) overproduced early RNA because of failure of the *tsA* protein (T antigen) to inhibit early transcription. The amount of early RNA in the cytoplasm, determined quantitatively from the kinetics of hybridization to labeled complementary SV40 DNA, was elevated at both permissive (32 C) and nonpermissive (41 C) temperatures in all the early mutants tested (*tsA*7, -30, -58, and -209), but not in the late mutant *tsB*4. The amount of early RNA in a culture maintained at 32 C for 72 hr and then shifted to 41 C was max when each cell was infected initially with at least one plaque-forming unit of *tsA*58. Azidocytidine (2'-deoxy-2'-azidocytidine), which inhibits initiation of DNA synthesis, did not cause overproduction of early RNA in cells infected with wild-type SV40, showing that the effect *tsA* mutants was due to interference with initiation of DNA synthesis per se. In parallel infections at 41 C, the amount of early RNA per copy of viral DNA was as much as 2,000 times greater with *tsA*58 than with wild-type SV40, even though there was no replication of *tsA*58 DNA. Synthesis of late RNA was not detected during the first 20 hr of infection by either virus at 32 C, indicating that late and early transcription are under different control. In three cell lines transformed by *tsA* mutants, the amount of early RNA increased moderately after a shift from 32 to 41 C; however, with homologous cells transformed by wild-type virus, the amount of early RNA decreased, indicating that the A protein may repress transcription of integrated SV40 DNA. All the observations are consistent with a simple model in which the binding of

protein at the origin of replication blocks binding of RNA polymerase to the early promoter or its progress through the early gene(s). (26 refs.)

77-6421 Characterization of the Myosin-phosphorylating System in Normal Murine Astrocytes and Derivative SV40 Wild-Type and A-Mutant Transformants. (Eng) Scordilis, S. P. (Section on Molecular Cardiology, Cardiology Branch, Natl. Heart, Lung, and Blood Inst., NIH, Bethesda, MD 20014); Anderson, J. L.; Pollack, R.; Adelstein, R. S. *J Cell Biol* 74(3): 940-949; 1977.

Myosin content and the myosin-phosphorylating system were examined in normal murine astrocytes (NMB) and in astrocytes transformed by wild-type simian virus 40 (SV40) (SVWT-MB) and by a temperature-sensitive (ts) A mutant of SV40 (A239-WB). In addition, the presence of stress fibers that stain with antiactin antibodies was determined. The prominent network of cytoplasmic fibrils (stress fibers) in the NMB cells stained brightly with fluorescent antibody to actin, suggesting an ordered contractile protein system. Cells displaying transformed growth showed a diffusely staining actin matrix without the long, well-developed fibers, suggesting a redistribution rather than a lower concentration of actin in the transformed cell. Actinomycin, myosin, and myosin light-chain kinase were isolated and purified from whole normal mouse brain and NMB, SVWT-MB, and A239-MB cultures. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of the astrocyte myosins revealed a heavy chain of 200,000 daltons and two light chains of 20,000 and 15,000 daltons, similar to other cytoplasmic myosins. The 20,000-dalton light chain could be phosphorylated by an endogenous myosin light-chain kinase with properties similar to those of the myosin light-chain kinase in human platelets but distinct from striated muscle myosin light-chain kinase. No differences were detected in either the astrocyte myosins or myosin light-chain kinases between normal and transformed cells, between transformed cells grown at the permissive and nonpermissive temperatures, or between SV40 wild-type and A-mutant transformants. (38 refs.)

77-6422 Inhibition of Viral Protein Synthesis in Monkey Cells Treated with Interferon Late in Simian Virus 40 Lytic Cycle. (Eng) Yakobson, E. (Dept. Virology, Weizmann Inst. Science, Rehovot, Israel); Prives, C.; Hartman, J. R.; Winocour, E.; Revel, M. *Cell* 12(1): 73-81; 1977.

BSC-1 cultures were exposed to monkey interferon (100 U/ml) 18 hr before or 21 hr after infection with simian virus 40 (SV40, 25 plaque-forming U/cell). Pretreatment with interferon reduced the amount of early SV40 RNA, but treatment late in the lytic cycle did not inhibit viral RNA synthesis. Viral 19S and 16S RNA species were undiminished in quantity and poly(A) content. How-

ever, despite the apparent normalcy of viral RNA classes, there was a marked reduction in the synthesis of their protein products (T antigen and capsid polypeptides). The association of viral RNA with heavy polyribosomes was strongly reduced. On the other hand, there was no degradation of nonviral polyribosomes, and the synthesis of most cellular proteins continued. These experiments demonstrate that late in infection, interferon inhibits viral messenger RNA translation. (39 refs.)

77-6423 Histones: Metabolism in Simian Virus 40-infected Cells and Incorporation into Virions. (Eng.) Tan, K. B. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA 19104). *Proc Natl Acad Sci USA* 74(7): 2805-2809; 1977.

The pattern of histone metabolism in cells lytically infected with simian virus 40 (SV40) and the histone composition of the virions were examined. Confluent African green monkey kidney (AGMK) cells were infected with 50 plaque-forming units of SV40 per cell. Cellular DNA replication in both mock- and virus-infected cells reached a max at 17 hr but began declining at 41 hr, the time of max viral DNA replication. The histone content per cell of mock-infected cultures remained almost constant. The histone content of virus-infected cells increased dramatically at late times after infection and between 41 and 53 hr, each cell contained 2.7x as much histones as did each mock-infected cell. After 60 hr, the cells showed severe cytopathic effects and a loss of histones. The synthesis of all five host histone species was induced after virus infection, and they appeared to be more highly phosphorylated than their counterparts in the mock-infected cells. During the course of infection, the different histones were synthesized in the same relative amounts and in proportions similar to those obtained from mock-infected cells. During the later stages of infection, synthesis of histones and viral DNA in the virus-infected cells was coordinated. All the histone species except H1 were incorporated into virions. Compared to cellular histones, virion histones were enriched in the arginine-rich species H3 and H4. Both old and newly synthesized cellular histones were incorporated into virions, but there were about 5x more newly synthesized than old histone polypeptides in the virions. Virion DNA, which represents a newly synthesized DNA moiety in the infected cell, is associated predominantly with new histones. The induction of histone synthesis in SV40-infected cells is therefore important for providing new histones for virion formation. (34 refs.)

77-6424 DNA Polymerase Activities in Growing Cells Infected with Simian Virus 40. (Eng.) Mechali, M. (Unite Enzymologie, Institut de Recherches Scientifiques sur le Cancer, B. P. No. 8, 94800 Villejuif, France); Girard, M.; De Recondo, A. M. *J Virol* 23(1): 117-125; 1977.

DNA polymerase α , β , and γ levels were determined in the cytoplasm, nuclear Triton wash, and nucleus of growing CV₁ cells before and during infection with simian virus 40 (SV40). There was no significant change of any of the polymerase activities in the cytoplasmic fraction after infection with SV40. However, the activity of DNA polymerase α was increased about fourfold in the nuclear membrane extracts (Triton wash) and about threefold in the nuclear extracts early (15 hr) after infection. DNA polymerase β activity was increased approx twofold in the nuclear membrane extract and threefold in the nuclei. The activity of DNA polymerase γ , which was very low, varied somewhat, similar to polymerase β . These activities (α , β , γ) remained elevated only in the nuclei at 39 hr postinfection. The transient increase in the nuclear membrane extracts may represent the formation of membrane-attached SV40 DNA replication complexes or the migration of polymerase molecules from the cytoplasm to the nucleus. The results suggest that DNA polymerase α might be the major enzyme involved in SV40 DNA replication. (31 refs.)

- 77-6425 **Properties of Simian Virus 40 Transcriptional Intermediates Isolated from Nuclei of Permissive Cells.** (Eng.) Shani, M. (Lab. Biology Viruses, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD 20014); Birkenmeier, E.; May, E.; Salzman, N. P. *J Virol* 23(1): 20-28; 1977.

A nucleoprotein complex that is a viral transcriptional intermediate (TI) was isolated from simian virus 40 (SV40)-infected African green monkey cells (BSC-1) and partially characterized. The TI's sedimented in neutral sucrose gradients with a peak of about 24S to 26S and contained DNA, DNA-dependent RNA polymerase II, and nascent RNA chains. The TI's were capable of synthesizing RNA in vitro when supplied with substrates. This RNA was extremely heterogeneous in size, with a range of 4S to about 20S. Hybridization of the product RNA with SV40 DNA I and with restriction (*Hind*) fragments revealed that at least 70% of the RNA is virus-specific, with 90% complementary to the L strand and 10% complementary to the E strand. (19 refs.)

- 77-6426 **Antigenic Similarity Between Simian Virus 40-induced Surface and Fetal Antigens in Hamster Cells.** (Eng.) Kato, K. (Dept. Enteroviruses, Natl. Inst. Health, Kamiosaki, Shinagawa-ku, Tokyo 141, Japan). *J Natl Cancer Inst* 58(2): 259-262; 1977.

The tumor-associated cell-surface antigen (TSSA) on simian virus 40 (SV40)-transformed hamster cells was studied serologically by a complement-dependent cytotoxicity test. Antiserum was obtained from guinea pigs inoculated with SV40-transformed hamster cells. The serum was cytotoxic to SV40-transformed hamster cells after absorption with 15-day ham-

ster embryo cells (HEC), hamster cells transformed by either polyoma virus or adenovirus 12, various tissues of hamster origin (brain, kidney, and spleen), or sheep RBC. The cytotoxicity was eliminated from the serum after absorption with hamster cell lines transformed in vivo or in vitro with SV40, or by absorption with 11- to 12-day HEC. The cytotoxicity was not eliminated by absorption with 13- or 15-day HEC. These results indicate that the major SV40 TSSA is of fetal origin. (31 refs.)

- 77-6427 **Subcellular Distribution of the Tumor-specific Transplantation Antigen of Simian Virus 40-Transformed Cells.** (Eng.) Rogers, M. J. (Lab. Cell Biology, NCI, NIH, Public Health Service, U.S. Dept. Health, Education and Welfare, Bethesda, MD 20014); Law, L. W.; Appella, E. *J Natl Cancer Inst* 59(4): 1291-1295; 1977.

Pure nuclei and plasma membranes were isolated from Simian virus 40 (SV40)-transformed fibroblasts of Balb/c origin designated as mKSA (TU-5) and a subline designated mKSA (ASC) in order to obtain a quantitative estimate of their transplantation antigen (TSTA) activity. It was shown that nuclei and crude membranes contained equal amounts of T-antigen by complement fixation tests. However, the nuclei were far more effective than crude plasma membranes in protecting against challenge with mKSA (ASC) transplantable sarcoma. None of the nuclear preparations protected against two other syngeneic tumors of Balb/c mice, the chemically-induced Meth A and Adj PC5, which have their own specific TSTA. These results suggest that most of the TSTA is associated with the nuclear fraction. Such data support the hypothesis that when the early region of the infecting SV40 genome is translated in the cytoplasm and the polypeptide product is transported to the plasma membrane, an additional unspecified processing step may result in the loss of T-antigen by retention of TSTA. (23 refs.)

- 77-6428 **Biology of Simian Virus 40 (SV40) Transplantation Antigen (TrAg). II. Isolation and Characterization of Additional Temperature-sensitive Mutants of SV40.** (Eng.) Tevethia, M. J. (Dept. Pathology, Tufts Univ. Sch. Medicine, Boston, MA 02111); Ripper, L. W. *Virology* 81(2): 192-211; 1977.

Fourteen temperature-sensitive (*ts*) mutants of simian virus 40 (SV40) were isolated following mutagenesis by nitrous acid or hydroxylamine. The mutants were partially characterized by complementation assays and immunological detection of marker antigens. Three main complementation groups were assigned: A, B, C, and D, with some tests showing complementation between B and C. The *tsA* and *tsD* mutants were defective in their ability to synthesize infectious DNA at the nonpermissive temperature (41°C). Since the A group

been found to produce the initiator protein for viral NA replication, it was suggested that this gene might also code for the intranuclear tumor (T) antigen. All the *ts* A mutants failed to synthesize late antigens. The *ts* D mutants are defective in uncoating, and, hence, defective in the production of T antigen and late antigens. Most of the *ts* BC mutants produced the late antigens (capsid, virion, and major capsid protein antigens), but a few did not synthesize virion antigen. (37 refs.)

6429 **Biology of Simian Virus 40 (SV40) Transplantation Antigen (TrAg). III. Involvement of SV40 Gene A in the Expression of TrAg in Permissive Cells.** (Eng.) Tevethia, M. J. (Dept. Pathology, Tufts Univ. Sch. Medicine, Boston, MA 02111); Tevethia, S. S. *Virology* 81(2): 212-223; 1977.

Temperature-sensitive (*ts*) mutants of simian virus 40 (SV40) are used to help clarify the role of the viral genome in the expression of SV40-specific transplantation rejection antigen (TrAg). The ability of wild-type (*wt*) SV40 and SV40 *ts* mutants belonging to complementation groups A, B, BC, C, and D to induce the expression of TrAg at the surface of infected permissive African green monkey kidney cells was determined. At the restrictive temperature (41°C), *ts* A mutants are defective in inducing TrAg in these cells. However, the mutants did express SV40-TrAg at the permissive temperature (33°C). Therefore, SV40 gene A is involved in the expression of TrAg in SV40-infected permissive cells. The physical relationship of TrAg with tumor antigen remains unclear, in spite of the fact that the A gene controls the expression of other antigens. (39 refs.)

6430 **Differences Between the Structural Dynamics of Plasma Membranes of Normal Hamster Lymphocytes and Lymphoid Cells Neoplastically Transformed by Simian Virus 40 as Revealed by Laser Raman Spectroscopy.** (Eng) Verma, S. P. (Dept. Therapeutic Radiology, Radiobiology Div., Tufts-New England Medical Center, Boston, MA 02111); Schmidt-Ullrich, R.; Thompson, W. Wallach, D. F. *Cancer Res* 37(10): 3490-3493; 1977.

Laser Raman spectra of highly purified plasma membranes from simian virus 40 (SV40)-transformed GD248 lymphocytes were compared with those of the membranes of normal cells over the region 100 to 3010/cm⁻¹. Striking differences between the two membrane categories were observed in the thermal response of the CH-stretching and acoustical vibrations. Analysis of CH-stretching showed that the normal membranes exhibited a thermal transition centered at 7°C, approx 5°C wide. The membranes of GD248 cells, in contrast, showed a lipid transition centered at -5 and 12-18°C wide. Analysis of the acoustical region yielded equivalent results. The membrane proteins of normal membranes under-

went a large thermotropic transition, starting at 39°C (sample temperatures); with GD248 plasma membranes, this transition began at 23°C. The results suggest the possibility that SV40-specific membrane proteins may modify the collective thermotropic behavior of both normal membrane proteins and membrane lipids. (29 refs.)

77-6431 **The Characterization of SV40-transformed Cell Lines Derived from Mouse Teratocarcinoma: Growth Properties of Differentiated Characteristics.** (Eng) Topp, W. (Cold Spring Harbor Lab., Cold Spring Harbor, NY 11724); Hall, J. D.; Rifkin, D.; Levine, A. J.; Pollack, R. *J Cell Physiol* 93(2): 269-276; 1977.

Tumor cells from the transplantable OTT 6050A teratocarcinoma were harvested from the peritoneal cavity of 129Vsl mice and cultured in vitro. One month after these cultures were established, they were infected with 0.25 ml of simian virus 40 [SV40: 10⁸ plaque-forming units (PFU)/ml] at a rate of 30 to 100 PFU/cell. Thirty-one cell lines were isolated. All 31 lines contained SV40 tumor (T) antigen; with one exception, > 95% of the cells contained T antigen. The morphology of each of these lines was distinct. The criteria for SV40 transformation were: doubling times in medium with 1% serum that do not exceed two times the generation time in 10% serum; formation of colonies on top of a cell monolayer with at least 5% of the efficiency of plating on plastic surfaces; and ability to form colonies in methocel with efficiencies at least 1% of those on plastic surfaces. Twenty-one lines satisfied the first criterion, 19 the second, and 6 the third. Only three were transformed with respect to all criteria; two were not transformed by any criteria. Injection (sc or ip) of cells from any line into mice did not result in any tumor formation over a 7- to 8-mo period. Assays for plasminogen activator and creatine phosphokinase indicated that the two enzyme activities were expressed independently of each other. These lines may be helpful in tracing teratocarcinoma development in vitro. (34 refs.)

77-6432 **Effect of SV40 Infection of [³H]Uridine Incorporation.** (Eng) Ho-Terry, L. (Dept. Bacteriology, Univ. Coll. Hosp. Medical Sch., University St., London WC1E 6JJ, England); Cohen, A. *Biochem Biophys Acta* 479(1): 24-30; 1977.

A study was made of ³H-uridine incorporation in simian virus 40 (SV40)- and mock-infected CV-1 African green monkey kidney cells in relation to the specific activity of the precursor nucleotide uridine triphosphate (UTP). More ³H-uridine was incorporated into the RNA of SV40-infected cells than into that of uninfected cells 31 hr after infection. When the specific activity of the UTP pools in infected and uninfected cells was equated by the addition of appropriate amounts of exogenous unlabeled uridine, there was no difference in ³H-uridine

incorporation rate into RNA. Although no difference in ³H-uridine entry or phosphorylation was demonstrable, the apparently smaller pools of endogenous RNA precursors in infected cells resulted in less isotope dilution and thus led to synthesis of UTP and RNA of higher specific activity. (12 refs.)

77-6433 Genetic Analysis of Host Range Mutant Viruses Suggests an Uncoating Defect in Simian Virus 40-resistant Monkey Cells. (Eng.) Wilson, J. H. (Marrs McLean Dept. Biochemistry, Baylor Coll. Medicine, Houston, TX 77030). *Proc Natl Acad Sci USA* 74(8): 3503-3507; 1977.

Host range mutations that permit simian virus 40 (SV40) to grow with increased efficiency on SV40-resistant monkey cells were examined using a new mapping method that relies on the coupling of specific DNA fragments. Pairs of restriction endonucleases that cleave SV40 DNA at only one site were used to generate pairs of specific DNA fragments. Corresponding fragment pairs were purified from host range mutant and wild-type DNA and joined in known combinations to determine the location of the host range mutations. The results indicated that the mutations responsible for the phenotype of the host range viruses studied are located between 0.00 and 0.14 on the standard SV40 physical map, a region entirely within the B/C gene, which codes for the major capsid protein of the virus. The map position of the host range mutations was confirmed by using the same technique

to generate and couple genetically marked viral DNA fragments to produce the predicted double mutants. Three different double mutants were constructed that carried both host range and temperature-sensitive A mutations. Fragment coupling of these mutants confirmed that the mutation responsible for the host range virus phenotype was in the B/C gene. The mutations in these three different host range mutants appear to affect closely linked, perhaps identical sites, because wild-type virus was not detected among the progeny produced by infecting cells with pairwise heteroduplexes between them. The genetic analysis of the host range viruses is consistent with a previous physiological analysis of the resistant cells and with the interpretation that these cells are defective in their ability to uncoat SV40. (21 refs.)

See also:

*(Rev.): 77-6085, 77-6086, 77-6087, 77-6088, 77-6089, 77-6090, 77-6091, 77-6104, 77-6108, 77-6111.

*(Chem.): 77-6178, 77-6197, 77-6242.

*(Immun.): 77-6435, 77-6436, 77-6438, 77-6439, 77-6440, 77-6441, 77-6448, 77-6453, 77-6464, 77-6466, 77-6467, 77-6481, 77-6482, 77-6483, 77-6484, 77-6487, 77-6495, 77-6496.

*(Path.): 77-6508, 77-6553, 77-6557, 77-6559, 77-6560, 77-6565.

*(Epid.-Biom.): 77-6586, 77-6587.

IMMUNOLOGY

77-6434 **Comparison of Three Isotopic Assays of Cell-mediated Cytotoxicity Against Mouse Tumor Cells. I. Basic Parameters: Baseline Controls, Target Cells, and Methods of Calculation.** (Eng) Ting, C. C. (Lab. Cell Biology, NCI, NIH, Bethesda, MD 20014); Park, J. Y.; Nunn, M. E.; Herberman, R. B. *J Natl Cancer Inst* 58(2): 323-330; 1977.

Three isotopic assays of cell-mediated cytotoxicity (^{51}Cr -release assay, ^{125}I -iododeoxyuridine-release assay, and ^3H -proline-release assay) were compared under identical test conditions with respect to baseline controls, preparation of target cells, and methods of calculation. Comparisons were made in syngeneic and allogeneic mouse tumor systems. Normal baseline controls gave the most consistent results, and the other two controls evaluated (autologous and medium controls) gave varying results depending upon the condition of the target cells. Compared to fresh ascites tumor cells or short-term tissue culture cells, established tissue culture cells were usually superior as target cells because of a much lower spontaneous release of the isotope. The advantage of established culture cells was particularly pronounced in isotopic assays with prolonged incubation periods (20-40 hr). Comparison of calculation methods indicated that for conservative estimates of immune reactivity, it is more appropriate to calculate the net percent release relative to total radioactivity rather than to compare the radioactivity remaining in the test and control samples. (27 refs.)

77-6435 **The Mononuclear Cell in Human Blood Which Mediates Antibody-dependent Cellular Cytotoxicity to Virus-infected Target Cells. I. Identification of the Population of Effector Cells.** (Eng) Shore, S. L. (Virology Div., Center Disease Control, Public Health Service, Atlanta GA 30333); Melewicz, F. M.; Gordon, D. S. *J Immunol* 118(2): 558-566; 1977.

Mononuclear cells from human blood of healthy adults with no history of recurrent cold sores were fractionated by physical and immunologic techniques, and the resulting cellular subpopulations were assessed for their capacity to lyse herpes simplex virus (HSV)-infected target cells in the presence of IgG antibody to HSV. Latex phagocytosis and surface marker studies were also performed to identify the major effector cells by their phagocytic properties and their possession of surface immunoglobulin and receptors for sheep RBC, C3, or the Fc fragment of IgG. Cytotoxic effector cell activity was

unaffected or slightly enhanced after the removal of plastic-adherent or carbonyl iron-adherent mononuclear cells, indicating that the major effector cell is not a classic monocyte. Similar results were obtained after removal of > 90% of the T cells or > 95% of the B cells. Effector cell function was also normal in three patients with B-cell-deficient X-linked agammaglobulinemia. A four- to fivefold enrichment in effector cells, however, was consistently found in a subpopulation, consisting of 5% of the unfractionated mononuclear cells, that was enriched for both nonphagocytic cells with only Fc receptors (K cells) and nonphagocytic cells with no detectable surface markers (null cells). These and other studies lead to the conclusion that the major mononuclear effector cell in human blood is a K cell. (61 refs.)

77-6436 **The Mononuclear Cell in Human Blood Which Mediates Antibody-dependent Cellular Cytotoxicity to Virus-infected Target Cells. II. Identification as a K Cell.** (Eng) Melewicz, F. M. (Parasitology Div., Center Disease Control, Public Health Service, Atlanta, GA 30333); Shore, S. L.; Ades, E. W.; Phillips, D. J. *J Immunol* 118(2): 567-573; 1977.

Experiments were conducted to determine whether the mononuclear cell in human blood that mediates antibody-dependent cellular cytotoxicity (ADCC) to herpes simplex virus (HSV)-infected target cells has surface Fc receptors that participate in the reaction. The F(ab')_2 fragment of human IgG antibody (obtained by pepsin digestion of human γ -globulin) was inactive in both ADCC and complement-mediated cytotoxicity, but it retained the capacity to neutralize infectious virus, agglutinate sheep RBC coated with viral antigens, and bind to the surface of virus-infected cells. Treatment of sensitized virus-infected target cells with staphylococcus protein A, which has affinity for the Fc epitope of IgG, strongly reduced their susceptibility to lysis by ADCC in a dose-dependent manner. These findings indicate that the Fc portion of IgG antibody to the virus is necessary for cytotoxicity. Treatment of blood mononuclear cells with either heat-aggregated γ -globulin or HSV immune complexes inhibited effector cell activity. The presence of third-party cellular immune complexes also inhibited ADCC. Adsorption of mononuclear cells to plastic surfaces coated with soluble third-party immune complexes reduced effector cell activity significantly. It is concluded that the ADCC effector cell possesses surface Fc receptors that are utilized in the ADCC reaction. The presence of Fc receptors on the surface

of the effector cell indicates that it is a K cell rather than a null cell. (30 refs.)

- 77-6437 **A Comparison of Antibody-dependent Cellular Cytotoxicity (ADCC) Mediated by Murine and Human Lymphoid Cell Populations.** (Eng) Berger, A. E. (Dept. Microbiology and Immunology, Div. Immunology, Duke Univ. Medical Center, Durham, NC 27710); Amos, D. B. *Cell Immunol* 33(2): 277-290; 1977.

Since mouse lymphoid cells are known to lyse chicken red blood cells (CRBC) in the presence of antibody and the absence of complement and to effect the lysis of mouse tumor cells and other nucleated targets, studies were carried out to extend the number of known sources of effector cells and target tissues from various mouse strains. A 4-hr ^{51}Cr -release assay was used to compare the activity of mouse effector cells from the thymus, spleen bone marrow, peritoneal cavity, and mesenteric and subcutaneous lymph nodes of many mouse strains with the activity of human lymphoid cell effectors against chicken red blood cells (CRBC) and a number of murine targets. Human effector cells mediated the lysis of all targets tested. Mouse effector cells lysed CRBC but less effectively than the human cells. Mouse cells from lymphoid organs were very inefficient or completely inactive against nucleated mammalian targets under a range of test conditions. In experiments in which cells from solid lymphoid organs or the peritoneal cavity were ineffective, peripheral blood lymphocytes from one DBA/2 subline consistently gave significant lysis of EL4 targets, although cells from another subline of the same strain did not. (38 refs.)

- 77-6438 **Antibody-dependent Cellular Cytotoxicity (ADCC) Against Epstein-Barr Virus-determined Antigens. III. Reactivity in Sera from Patients with Burkitt's Lymphoma in Relation to Tumour Development.** (Eng.) Jondal, M. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Gunven, P. *Clin Exp Immunol* 29(1): 11-15; 1977.

Sera for patients with Burkitt's lymphoma (BL) were tested for antibody-dependent cellular cytotoxicity (ADCC) against Epstein-Barr virus (EBV)-determined antigens and for antibodies directed against EBV-specific membrane antigens (MA), viral capsid antigens (VCA), and early antigens (EA). No correlation was found between EBV serology and ADCC in sera selected for high or low titers against the MA or in consecutive sera from three patients with isolated late tumor recurrences. Anti-VCA and -EA titers have a considerable range between and within the patients, but they do not correlate appreciably with ADCC titers. Furthermore, there was no correlation between ADCC and tumor development. EBV neutralization may depend upon the presence of addi-

tional antigenic specificities on the viral particles, thus allowing even the low anti-MA-titered sera to form immune complexes with EBV, inducing ADCC. Formation of anti-MA antibodies most probably depends upon differentiation toward virus production, a process that kills the host cell and thus is incompatible with tumor growth. (20 refs.)

- 77-6439 **In Vitro Lysis of Tumor Cells by Antibody and Complement: Detection of Antibody with Labeled Complement and Cytotoxic Reactivity.** (Eng) DiSciullo, S. O. (Dept. Microbiology, Univ. Rhode Island, 318 Morrill Hall, Kingston, RI 02881); Laux, D. C. *J Natl Cancer Inst* 59(6): 1631-1637; 1977.

Factors affecting the in vitro lysis of antibody- and complement-mediated PARA-7 tumor cells were examined by the ^{51}Cr -release assay. These cells were obtained by the in vitro transformation of hamster embryo fibroblasts by defective simian virus 40-adenovirus 7. The addition of immune syngeneic hamster antisera (HA) to ^{51}Cr -labeled PARA-7 target cells 30 min before the addition of guinea pig complement (GPC) failed to produce significant levels of lysis. Similarly, the addition of rabbit anti-PARA-7 serum (RAS) 30 min prior to the addition of GPC resulted in low levels of lysis. Longer incubations in the presence of RAS, but not RAS alone, increased lysis. Extended incubation in the presence of RAS increased the amount of antibody bound to the target cells. This increase did not appear to be due to the expression of additional antigen, because it occurred at 4°C and was not sensitive to inhibitors of protein synthesis. The inability to obtain increased levels of lysis by extended incubation in the presence of both RAS and GPC appeared to be due to the inhibitory effects of GPC on antibody-antigen interaction. Similar inhibitory effects could be produced by inactivating GPC and various other substances. When extended incubations in the presence of antiserum were used for reexamination of the cytolytic activity of syngeneic immune HA, significant lysis was detectable. (17 refs.)

- 77-6440 **Detection of Complement-dependent Lytic Antibodies in Sera from Feline Leukemia Virus-infected Cats by the Chromium-51 Release Assay.** (Eng) Grant, C. K. (Dept. Surgery, Section Clinical Oncology, School of Veterinary Medicine, Univ. California, Davis, CA 95616); Worley, M. B.; DeBoer, D. J. *J Natl Cancer Inst* 58(1): 151-161; 1977.

Sera from cats naturally infected with feline leukemia virus (FeLV) contained complement-dependent antibodies that lysed FeLV-infected FL74 cells. The lysis was detected by the ^{51}Cr -release method; it was mediated by serum complement from both rabbits and guinea pigs. Preliminary data suggest a partial correlation between results obtained by immunofluorescence and those obtained by ^{51}Cr release. (11 refs.)

77-6441 **Antibody Response to Simian Virus 40 Tumor Antigen in Nude Mice Reconstituted with T Cells.** (Eng.) Cicurel, L. (Wistar Inst. Anatomy and Physiology, 36th St. at Spruce, Philadelphia, PA 19104); Croce, C. M. *J Immunol* 119(39): 850-854; 1977.

Genetically athymic BALB/c nude mice (nu/nu) were unable to produce antibodies against simian virus 40 (SV40) T antigen when immunized with SV40-transformed mouse cells or with SV40 T antigen-positive hybrids derived from SV40-transformed human and normal mouse cells. All nude mice developed solid tumors at the injection site. In contrast, immunocompetent BALB/c and C57BL/6 mice were able to generate a humoral immune response against SV40 T antigen and resist tumor development when immunized with SV40-transformed mouse cells or hybrids. However, reconstitution of nude mice with T cells by adoptive transfer of BALB/c lymphocytes or spleen-derived I cells allowed the nude mice to produce antibodies against the SV40 T antigen when immunized and, partially, to resist tumor development. The antiserum activity to SV40 T antigen was consistently higher in nude mice reconstituted with spleen-derived cells than in recipients restored with thymocytes. This may be due to the fact that the thymus still contains a certain number of immature cells, but the spleen has a larger population of antigen-recognizing mature cells. (16 refs.)

77-6442 **Characteristics of the Immature Cells Involved in T-cell-mediated Enhancement of Syngeneic Tumor Growth (Meeting Abstract).** (Eng) Small, M. (Weizmann Inst. Science, Rehovot, Israel). *Isr J Med Sci* 13(10): 1058; 1977. (no refs.)

77-6443 **Activation of Cytotoxic T Cells by Nonstimulating Tumor Cells and Spleen Cell Factor(s).** (Eng) Talmage, D. W. (Dept. Microbiology and Immunology, Univ. Colorado Medical Center, Denver, CO 80262); Woolnough, J. A.; Hemmingsen, H.; Lopez, L.; Lafferty, K. *Proc Natl Acad Sci USA* 74(10): 4610-4614; 1977.

The ability of three cultured mouse tumor lines to stimulate a cytotoxic response in 5-day cultures of allogeneic lymph node cells was studied with a ^{51}Cr -release assay. The cell lines included the P815 mast cell tumor of DBA/2 mice, the EL-4 lymphoma from a C57BL/6 mouse ascites tumor, and carcinoma D2 (CaD2), a mammary tumor of DBA/2 mice. The two lines of mesenchymal origin, P815 and EL-4, were highly stimulatory, but CaD2 showed no stimulating activity over a wide range of cell concentrations. UV-irradiated P815 cells, like γ -irradiated CaD2 cells, did not stimulate a cytotoxic response, but both cell lines stimulated a full and specific response to allogeneic lymph node cells when the mixed

cultures were supplemented with a supernatant harvested from concanavalin A-stimulated spleen cells. This failure of CaD2 to stimulate allogeneic lymphocytes was not due to a lack of surface histocompatibility antigen (H-2), since C57BL/6 lymphocytes activated against H-2d antigens on irradiated DBA/2 spleen cells were cytotoxic for both ^{51}Cr -labeled CaD2 and P815 tumor cells. (20 refs.)

77-6444 **Induction in B2/B2 Chickens of Immunity to Transplantable Carcinogen-induced Fibrosarcomas Mediated by T-Cell Monocyte Cooperation: Role of Delayed Hypersensitivity to Unrelated Antigens.** (Eng) Palladino, M. A. (Dept. Pathology, New York Univ. Medical Center, 550 First Ave., New York, NY 10016); Thorbecke, G. J. *Adv Exp Med Biol* 88: 331-343; 1977.

Immunity to dimethylbenzanthracene-induced fibrosarcomas from SC chickens (SCFS) was induced in histocompatible *Corynebacterium parvum*- or BCG-pretreated chickens by injection of SCFS cells with *C. parvum* or BCG into the wing webs. Splenic T cells from these chickens, which rejected subsequent SCFS transplants, showed tumor immunity with a specificity for the immunizing SCFS line. Normal monocytes restored the immunocompetence of birds that could not express tumor immunity after pretreatment with silica (6 mg, iv), γ radiation (1,260 R), and trypan blue. Furthermore, tumor growth was inhibited by delayed hypersensitivity reactions to unrelated antigens, such as human γ globulin or to *C. parvum*, according to a similar effector cell mechanism. It was concluded that in the chicken, cooperation between immune T cells and normal monocytes results in tumor growth inhibition at the tumor site both when the antigen resides on the tumor cell itself and when an unrelated additional antigen is injected concomitantly with the tumor cells. Tumor-specific immunity may result from these locally occurring reactions. (17 refs.)

77-6445 **Selective Mobilization of Specifically Cytotoxic T-Lymphocytes at Sites of Inflammation in Relation to BCG-induced Resistance to Implants of Syngeneic Sarcoma in Mice.** (Eng) Parr, I. B. (Div. Tumour Immunology, Chester Beatty Res. Inst., Clifton Ave., Belmont, Sutton, Surrey SM2 5PX, England); Wheeler, E.; Alexander, P. *J Natl Cancer Inst* 59(6): 1659-1666; 1977.

Live BCG (300 μg) injected ip enhanced the resistance of C57BL/6 mice of both sexes to ip or iv challenge with 10^5 cells of syngeneic benzo(a)pyrene-induced sarcomas. The tumor grew normally when injected id or sc, and administration of BCG by other than the ip route had little or no effect on tumor growth. The specific cytotoxicity of peritoneal T cells and the total number of T cells recovered from the peritoneal cavity were tenfold greater in mice that had received BCG

ip 2-4 wk prior to tumor inoculation than in non-BCG-treated mice. The specific T cell-mediated cytotoxic potential of the peritoneal exudate of mice immunized with tumor was, therefore, at least 100 times greater in mice given BCG ip. This effect was detectable by 3 days after BCG inoculation and reached a max 2-4 wk later. The protection against tumor offered by pretreatment with BCG could be explained by the selective recruitment of committed T lymphocytes to sites of chronic inflammation. The induction of nonspecifically cytotoxic macrophages and systemic changes, such as generalized stimulation of the reticuloendothelial system, were not contributing factors. (29 refs.)

- 77-6446 Mechanisms of Impaired T-Lymphocyte Function in Sarcoidosis. (Eng.) Singal, D. P. (Host Resistance Programme, Dept. Pathology, McMaster Univ., Hamilton, Ontario, Canada); Alpers, J.; Clancy, R. *Prog Clin Biol Res* 16: 239-244; 1977.

The mixed lymphocyte culture (MLC) technique was used to study the lymphocytes obtained from two female patients (aged 23 and 24 yr) with sarcoidosis, one with an active form of the disease and one with a less active form. Two mechanisms of impaired peripheral T-lymphocyte function are suggested by the results of this study. First, selective redistribution of a subpopulation of peripheral lymphocytes with accumulation of MLC-reacting cells in abnormal lymph nodes was shown. Secondly, complete inhibition of a normal mixed lymphocyte reaction was induced by the addition of lymphocytes from the patient with active disease, indicating a cell-dependent inhibition of T-lymphocyte function. However, the nature of the suppressor cell population and the mechanism of inhibition are not clear from this experiment. (7 refs.)

- 77-6447 Increased Resistance to Established Tumor Metastases after Elimination of Thymus-T-Cell Mediated Suppression. (Eng) Falk, R. E. (Dept. Surgery, Univ. Toronto Faculty Medicine, Toronto, Canada); Nossal, N.; Samuel, E. S.; Falk, J. A. *Surg Forum* 28: 161-163; 1977.

Resistance to a transplantable dimethylcholanthrene-induced tumor was demonstrated in adult Fischer rats who had been thymectomized, irradiated with 950 rads, and repopulated with bone marrow cells from syngeneic rats. This resistance could be abrogated by spleen cells, thymocytes, or an avascular thymus graft. Therefore, in this tumor-host system, the major effect of the thymus and the peripheral cells is to suppress the antitumor function of B cells, macrophages, and, perhaps, a small T-cell subpopulation. (3 refs.)

- thylcholanthrene Tumors in Inbred Hamsters. (Eng) Blasecki, J. W. (Dept. Microbiology, Univ. Mississippi Medical Center, Jackson, MS 39216). *J Immunol* 119(5): 1621-1626; 1977.

Treatment of specifically sensitized MHA hamster lymphoid cells with rabbit antisera specific for hamster T-lymphocytes, in the presence of complement, eliminated those cells capable of inhibiting the growth of syngeneic simian virus 40 (SV40) and methylcholanthrene (MC) tumors in vivo. Thymectomized, lethally irradiated, bone marrow-reconstituted hamsters were, after attempted specific sensitization to the two syngeneic tumor cell lines, unable to reject either tumor by direct challenge in vivo. In addition, lymphocytes from these animals were incapable of inhibiting the growth of either tumor cell line in normal syngeneic recipients. These data strongly support the conclusion that specifically sensitized T-lymphocytes are required for the rejection of syngeneic SV40 and MC tumors in inbred hamsters. (27 refs.)

- 77-6449 Suppressor T Cells Arising in Mice Undergoing a Graft-vs-Host Response. (Eng) Pickel, K. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Hoffman, M. K. *J Immunol* 118(2): 653-656; 1977.

The ability of mice to generate antibody-forming cells during graft-vs-host (GVH) reaction was investigated by a semi-quantitative assay and various cell-separation techniques. Three spleen cell subpopulations were obtained: (1) one that contained predominantly T cells, (2) one that was T-cell depleted, (3) and one that was macrophage-depleted. The GVH reaction proceeded through two phases: an early phase in which antibody formation was enhanced and a later phase in which antibody formation was suppressed. The early (enhancing) phase was demonstrated best with the subpopulation 1. It was obscured by the presence of suppressor cells in cultures of whole GVH spleen cells. Both the enhancing and suppressing effects were eliminated using subpopulation 2; therefore, they were attributed to T lymphocytes that became activated during the GVH response. Suppressor T cells differed from helper T cells in size and acted directly on antigen-reactive B cells. The suppressor T cell induced in the GVH reaction was derived from donor spleen cells, because suppression was abrogated after irradiation of donor spleen cells but not after irradiation of the recipient. Suppressor T cells were specifically directed against components of the H-2 region of the reciprocal parental strain in the hybrid F₁ mouse. Since the GVH-induced suppressor T cells were most effective when added during the first 24 hr of culture it is concluded that they inhibit the early proliferative response of B-cell precursors rather than their differentiation into antibody-secreting plaque-forming cells. (12 refs.)

- 77-6448 Thymus-derived Lymphocyte-dependent Rejection of Syngeneic Papovavirus (SV40) and Me-

- 77-6450 Evidence for a Similar or Common Mechanism for Natural Killer Cell Activity and Resistance

o Hemopoietic Grafts. (Eng) Kiessling, R. (Dept. Tumor Biology, Karolinska Inst., Stockholm, Sweden); Hochman, P. S.; Haller, O.; Shearer, G. M.; Wigzell, H.; Cudkiewicz, G. *Eur J Immunol* 7(9): 655-663; 1977.

The resistance of irradiated and nonirradiated F₁ mouse hybrids to parental grafts of normal or malignant hemopoietic cells (Hh system) and the natural killer cell (NK) activity against mouse lymphomas were investigated to see if there is a correlation between the two. The fourth week of life appeared to be the critical age for both the onset of NK cell activity and resistance to bone marrow (BM) grafts. Activity increased gradually and was max at 6 to 8 wk of age. Survival at 24 hr and/or function of NK cells was relatively insensitive to radiation injury, particularly when compared with that of other cell types in the spleen. Furthermore, B6C3F₁ mice given 100 μ Ci of ⁸⁹Sr 26 days before removal of the spleen had considerably less NK cell activity than controls. When 0.5 ml of heterologous antiserum directed against various mouse tissues was injected iv into B6C3F₁ mice 1 day prior to assay, splenic NK cell activity was markedly reduced. The effect was dose-dependent, and suppression was still detectable 7 days after the injection. These findings suggest that reduction of NK cell activity involves interference with the generation of NK cells, rather than direct cytotoxicity for antibody-coated NK cells. Iv injection of 3 or 4 mg silica particles into B6C3F₁ mice 18 hr prior to assay significantly reduced NK cell activity. Injection of 1 mg of ι -carrageenan caused an even greater reduction of NK activity. B6C3F₁ mice were also exposed to 900 rads of γ rays 1 hr prior to antimacrophage agents, and NK activity was measured 18 hr later. The spleen cells of nonirradiated and irradiated mice had the same NK cell activity, but the spleen cells of irradiated mice given silica particles, ι -carrageenan, or anti-BM serum had reduced activity. Multiple injections of parental spleen cells into F₁ mice reduced NK activity. These findings indicate that similar or identical mechanisms are responsible for Hh and NK activity. (46 refs.)

77-6451 **Transplantability and Metastasisability of An MCA-induced Sarcoma in Nude Mice: Influence of Transfer of Thymus Cells and Adoptive Immunity.** (Eng) Boeryd, B. (Dept. Pathology I, Regionsjukhuset, 581 85 Linköping, Sweden); Suurkula, M. *Acta Pathol Microbiol Scand [A]* 85(5): 745-750; 1977.

Nude (nu/nu) C57 mice were more resistant to sc and iv challenge with a methylcholanthrene-induced sarcoma from C57Bl/6J mice than were thymectomized, irradiated C57/(+/+) mice. The transfer of 5×10^7 thymus cells to the nude mice reduced their resistance to sc injected tumor cells to the level of that of the C57/(+/+) mice, but only when the tumor dose was 5×10^4 or 10^5 cells. A similar effect of thymus cells on iv injected tumor cells was suggested in some experiments. Spontaneous metastases did not occur in the C57 (nu/nu) mice and were possibly facilitated by specifically sensitized

spleen cells. The results indicate that the resistance of nude mice to sc injected tumors may depend on their inability to develop thymus-dependent immune responses and that spontaneous metastases can be facilitated by a weak immune response. (23 refs.)

77-6452 **Cell Transplantation into Immunodeficient Chicken Embryos: Reconstituting Capacity of Different Embryonic Cells.** (Eng) Eskola, J. (Dept. Medical Microbiology, Turku Univ., SF-20520 Turku 52, Finland); Toivanen, P. *Adv Exp Med Biol* 88: 39-45; 1977.

Chicken embryos were treated with three consecutive injections of cyclophosphamide (CP) on days 15, 16, and 17 of incubation. On day 18, the embryos were inoculated iv with 18-day-old embryonic bursa, spleen, bone marrow, thymus and liver cells, and the effects of transplantation were studied by morphological and functional criteria 4-6 wk after hatching. Only the bursa cells were capable of reconstituting the body and organ wts of the recipients or antibody formation against sheep RBC and Brucella. These cells also increased thymus wt and restored thymus morphology. In other experiments, 9-, 11-, 13-, 15-, and 18-day-old yolk sac cells were transplanted into CP-treated embryos. They had no effect on the morphology or immune functions of the recipients. These negative results suggest that CP destroys something crucial in the bursal microenvironment, rendering it unsuitable to harbor and educate the primitive stem cell. (11 refs.)

77-6453 **Immune Responses and Prevention of Lymphoid Leukosis Tumors in Chickens Fed an Androgen Analog.** (Eng) Romero, C. H. (U. S. Dept. Agriculture, Agricultural Res. Service, Regional Poultry Res. Lab., 3606 E. Mount Hope Road, East Lansing, MI 48823); Frank, F. R. *Adv Exp Med Biol* 88: 355-362; 1977.

Chickens of the cross of inbred lines 15 and 7, which are susceptible to infection by lymphoid leukosis virus (LLV), were infected at 1 day and 2 wk of age with a tumorigenic dose of two Rous-associated viruses (RAV-1 and RAV-2). Their diets consisted of 1.5 μ g/g basal feed of 17 β -hydroxy-7 α ,17-dimethylestr-4-en-3-one (Mibolerone) during the first 7 to 8 wk of life. To test its effect on naturally occurring LL tumors, commercial White Leghorn chickens naturally infected with field LLV's were given Mibolerone at concentrations of 1.0, 1.5, or 2.0 μ g/g basal feed during the first 7 wk of life. The androgen analog prevented the development of LL tumors in all birds tested. Tumor mortality in chickens infected with RAV-1, RAV-2, and field LLV was 71.8%, 42.3% and 25%, respectively, but the mortality in infected chickens fed Mibolerone was only 2.8%, 0%, and 0%, respectively. Necropsy demonstrated early bursa regression induced by the androgen analog. Mibolerone-treated chickens also remained fully immunocompetent to both inert and in-

fectious antigens, but they did not appear to have postbursal stem cells in their spleens. Mibolerone may be able to prevent LL in commercial poultry. (15 refs.)

- 77-6454 Effect of Different Cancer Treatment Methods on Immunity to an Antigenic Transplantable Murine Fibrosarcoma (Meth A).** (Eng.) Khafagy, M. (Dept. Surgery, Memorial Hosp., Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); Wanebo, H. J.; Alfieri, A.; Hahn, E. W. *Am J Roentgenol* 128(6): 1027-1029; 1977.

A study was conducted comparing the effects of excision, radiotherapy, cryosurgery, and tumor ligation on the tumor immunity of an antigenic chemically induced fibrosarcoma in female Balb/c mice. Results show that tumor-specific transplantation immunity to challenge with Meth A fibrosarcoma was not uniquely augmented by any of these methods of treatment. (15 refs.)

- 77-6455 Tumour-dormant States Established with L5178Y Lymphoma Cells in Immunized Syngeneic Murine Hosts.** (Eng) Weinhold, K. J. (Dept. Microbiology, Thomas Jefferson Univ., Philadelphia, PA 19107); Goldstein, L. T.; Wheelock, E. F. *Nature* 270(5632): 59-61; 1977.

Two tumor dormant states were established in DBA/2 mice using the methylcholanthrene induced lymphoma, L5178Y, of DBA/2 origin. In the first system, the mice were inoculated ip with 10^7 mitomycin C-treated L5178Y cells and, 10 days later, with live tumor cells. All nonimmunized mice died within 25 days of inoculation with 5×10^4 live cells, but no deaths occurred in the immunized challenged mice until day 60. By day 210, 93% of the mice had died of tumor. Tumor cells could be isolated from the peritoneal cavity and spleen of these mice during the normal period. Dormant tumor cells could be recovered from the peritoneal cavity as long as 380 days after challenge. In the second system, DBA/2 mice were inoculated sc with 1×10^6 L5178Y cells, and 10 days later the small (1-cm) tumor nodules were excised. Control mice thus treated remained tumor-free for 160 days. Excision of the tumor nodules protected mice against rapid outgrowths of 5×10^4 L5178Y cells inoculated ip 7 days later, but most of these animals developed tumors by day 160. Tumor cells could be isolated from the peritoneal cavity of many of the immunized and challenged mice while they were clinically normal. (14 refs.)

- 77-6456 Immunisation Against Chemically-Induced Rat Tumours (Meeting Abstract).** (Eng) Price, M. R.

(Cancer Res. Campaign Lab., Univ. Nottingham, Nottingham, England); Robins, R. A. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 90; 1977. (no refs.)

- 77-6457 Separation of Tumor-stimulating from Tumor-inhibiting Factors from Fetal and Adult Rat Tissues.** (Eng) Reichle, F. A. (Dept. Surgery, Temple Univ. Health Sciences Center, Philadelphia, PA); Noval, J. J.; Obando, M.; Reichle, R. M.; Ryzlak, M. T. *Surg Forum* 28: 169-171; 1977.

The effects of preparations of adult portacaval-shunted rat liver (SRL) or killed fetal tissue (KFT) on 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors were studied. At 10-20 wk after DMBA administration (10 mg), tumor frequency was significantly greater in rats that had also received whole homogenates or cytosol supernatants of SRL or KFT than in the DMBA controls. In contrast, a particulate sediment fraction of the SRL and KFT resulted in delayed tumor growth and a decrease in the number of tumors. The inhibition of tumor growth by this fraction may be due to the presence of cell membranes that are antigenically similar in fetal and tumor tissue. (3 refs.)

- 77-6458 Resistance to a Transplantable Lymphoma in BALB/c Mice (Meeting Abstract).** (Eng) Wedderburn, N. (Royal Coll. Surgeons England, London, England); Carter, R. L.; Campa, M. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 90; 1977. (no refs.)

- 77-6459 Inhibition of Tumor Growth by the Peptidoglycan from *Bacillus megaterium*.** (Eng) Nauciel, C. (Institut de Bacteriologie et d'Immunologie Generale, Faculte de Medecine, Universite Louis Pasteur, 3 rue Koeberle, 67000 Strasbourg, France); Goguel, A. F. *J Natl Cancer Inst* 59(6): 1723-1726; 1977.

When mixed with tumor cells and injected sc, the peptidoglycan extracted from *Bacillus megaterium* inhibited the growth of a methylcholanthrene-induced fibrosarcoma in syngeneic WAG rats. In some instances, tumor growth was totally suppressed. Animals rejecting mixed inocula exhibited a tumor-specific immunity, since they were resistant to a second challenge with tumor cells alone. The peptidoglycan was not cytotoxic for tumor cells; it rendered macrophages nonspecifically cytotoxic. (18 refs.)

- 77-6460 **Potential of Tumour Growth by Carrageenan.** (Eng) Thomson, A. W. (Dept. Pathology, Univ. Medical Buildings, Foresterhill, Aberdeen AB9 2ZD, Scotland); Fowler, E. F. *Transplantation* 24(5): 397-400; 1977.

To provide evidence for the role of macrophages in antitumor immunity, the effect of ip doses of carrageenan (a macrophage-toxic agent) on syngeneic adenocarcinoma development was studied in female C3H He mice. The animals received 10^6 viable tumor cells from a spontaneous tumor of virgin C3H He mice. Greatest potentiation of tumor growth by carrageenan was seen with four 1 mg injections the wk preceding tumor challenge. Single doses of 5 or 10 mg 24 hr prior to tumor challenge were less effective. When 1 mg was given 24 hr before tumor challenge and on the following days 3, 6, and 10, little effect was observed. Pretreatment with four 1 mg injections or the single 5 to 10 mg injection also caused a significant increase in tumor wt. The enhancement of tumor growth may be due to depletion of the functional macrophage population, allowing early tumor implantation and growth. (21 refs.)

- 77-6461 **Abrogation of Antitumor Effects of *Corynebacterium parvum* and BCG by Antimacrophage Agents.** (Eng) Keller, R. (Immunobiology Res. Group, Univ. Zurich, Schonleinstrasse 22, CH-8032, Zurich, Switzerland). *J Natl Cancer Inst* 59(6): 1751-1753; 1977.

Pretreatment of female DA rats with *Corynebacterium parvum* (3 mg) or BCG (10^8 cells) significantly increased their resistance to 7,12-dimethylbenz(a)anthracene-induced fibrosarcomas growing as localized sc tumors (10^3 - 10^4 cells, sc) or as ascites tumors (10^3 cells, ip). The antitumor effects of *C. parvum* and BCG were abrogated by the antimacrophage agents silica (10 mg, iv or ip) and carrageenan (5 mg, iv or ip). The results support the concept that macrophages may be involved in natural tumor resistance. (21 refs.)

- 77-6462 **Endocytosis of Red Blood Cells or Haemoglobin by Activated Macrophages Inhibits Their Tumoricidal Effect.** (Eng) Weinberg, J. B. (Div. Hematology/Oncology, Dept. Medicine, Univ. Utah Medical Center, Salt Lake City, UT 84148); Hibbs, J. B. *Nature* 269(5625): 245-247; 1977.

When tumoricidal macrophages (TM) from mice treated with BCG were allowed to phagocytose RBC, killing of 3T12 cells was inhibited completely at an RBC:TM ratio of 4:1. This inhibition was proportional to the RBC:TM ratio, with a less complete suppression of killing at ratios of 2:1 and 1:1, respectively. If serum syngeneic to the TM was present throughout the assay, no phagocytosis of RBC by TM occurred and there was no inhibition of tumor cell killing. As

long as the RBC were phagocytized, the tumoricidal effects were demonstrated. Heme-free globin inhibited tumor killing at levels of 500 to 1,000 $\mu\text{g/ml}$, once the globin particles were endocytosed by TM. Methemalbumin was inhibitory at levels of 500-2,000 $\mu\text{g/ml}$, but albumin lacking heme had no effect. Imferon (200-1,000 μg elemental iron/ml) or FeCl_3 or FeSO_4 (1-40 $\mu\text{g/ml}$) completely inhibited killing by TM if left throughout the assay, or used in a pretreatment manner. Non Hb RBC proteins did not inhibit killing, however. These results suggest that RBC, Hb, globin, and iron inhibit the tumoricidal effect of these activated macrophages. Therefore, pathologic conditions that produce excess amounts of RBC, Hb, or Hb degradation products within the macrophage vacuolar system could lead to a suppression of tumor cell killing and paralysis of the body's immune surveillance system. (32 refs.)

- 77-6463 **Reduction of Tumour Cell Entry into Vessels by BCG-activated Macrophages.** (Eng) Liotta, L. A. (Lab. Pathology, NCI, Bethesda, MD 20014); Gattozzi, C.; Kleinerman, J.; Saidel, G. *Br J Cancer* 36(5): 639-641; 1977.

In C57BL/6 mice bearing the highly metastatic, syngeneic T241 fibrosarcoma, the iv injection of BCG-activated peritoneal macrophages reduced the formation of pulmonary metastases. The reduction, which was significant when the macrophages were injected early after tumor transplantation, occurred in the absence of significant alterations in primary tumor size, proportion of necroses, or vascularity. Macrophages injected directly into the tumor mass did not reduce the number of metastases. These results support the hypothesis that iv-infused macrophages depress the entry of tumor cells into the vascular channels of the primary tumor. (11 refs.)

- 77-6464 **Generation of Macrophage Migration Inhibitory Activity by Plasminogen Activators.** (Eng) Roblin, R. O. (Basic Res. Program, Frederick Cancer Res. Center, Frederick, MD 21701); Hammond, M. E.; Bensky, N. D.; Dvorak, A. M.; Dvorak, H. F.; Black, P. H. *Proc Natl Acad Sci USA* 74(4): 1570-1574; 1977.

Overnight incubation of a serum-free harvest fluid (HF) from simian virus 40-transformed mouse 3T3 cells (SV3T3) in a medium with 15% guinea pig serum (GPS) at 37 C produced a medium that could inhibit the migration of guinea pig peritoneal exudate cells (macrophages). Examination of a ^3H -diisopropylfluorophosphate (Dip-F)-labeled SV3T3 HF preparation revealed a component with a mol wt expected of mouse cell plasminogen activator (ie, a serine protease). ^3H -Dip-F treatment led to approximately 95% inhibition of plasminogen activator activity and completely abolished its capacity to generate MIF-

like activity. The SV3T3 cell plasminogen activator apparently generates MIF-like activity upon interaction with a component of GPS. A purified preparation of human urokinase, a known plasminogen activator, was also capable of generating MIF-like activity when incubated in medium containing GPS. The possible effects of plasminogen activator secreted by tumor cells and MIF activity on macrophage function and consequent tumor growth warrant further investigation. (17 refs.)

- 77-6465 **Immune Adherence Reactivity of Rat Alveolar Macrophages Following Inhalation of Crocidolite Asbestos.** (Eng) Miller, K. (Dept. Immunology, Natl. Res. Inst. for Occupational Diseases, South African Medical Res. Council, Johannesburg, South Africa); Kagan, E. *Clin Exp Immunol* 29(1): 152-158; 1977.

The immune adherence phenomenon was used to demonstrate the in vivo deposition of complement on membranes of alveolar macrophages from outbred rats (*Rattus norvegicus*) chronically exposed to crocidolite asbestos dust (1,350 fibers/cm², 8 hr/day, 5 days/wk for 6 mo). Pretreatment of macrophage cultures with antiserum to complement 3 greatly diminished the level of immune adherence reactivity. Alveolar macrophages exposed to crocidolite asbestos in vitro did not exhibit significant levels of immune adherence reactivity. These results may reflect an in vivo antigen-antibody-complement interaction on the surface of alveolar macrophages from animals that have inhaled asbestos dust. (22 refs.)

- 77-6466 **The Role of Macrophages in Defense Against the Development of Rauscher Virus Leukemia.** (Eng) Knyszynski, A. (Section Biological Ultrastructure, Weizmann Inst. Science, Rehovot, Israel); Danon, D. *J Reticuloendothel Soc* 22(4): 341-348; 1977.

RBC obtained from SWR mice inoculated with Rauscher leukemia virus (RLV) and transfused into normal syngeneic mice disappeared from the circulation more rapidly and had a shorter life span than RBC from normal mice. The sequestered RBC from both normal and RLV-infected mice accumulated mainly in the spleen and liver of the transfused animal. There was a tenfold higher concentration of the label in the spleen and a threefold higher concentration in the liver when the transfused RBC originated from RLV-infected mice rather than from normal mice. Injection of colloidal carbon into the recipient animals prior to inoculation with plasma or RBC from RLV-infected mice made it possible to induce Rauscher leukemia even when dilute solutions of plasma (1:10³) were used. When RBC suspensions were injected to induce the disease, 10³ cells were sufficient. Similar results were obtained when a macrophage toxin, carrageenan, was injected prior to virus-containing plasma. The results

suggest that macrophages phagocytize RLV and sequester RBC from RLV-infected mice as 'deteriorated self' cells, like old RBC, and thus play a role in the defense against development of Rauscher leukemia. (2 refs.)

- 77-6467 **Post-infection Genetic Resistance to Avian Lymphoid Leukosis Resides in B Target Cells.** (Eng) Purchase, H. G. (Natl. Program Staff, Agricultural Res. Service, US Dept. Agriculture, Beltsville, MD 20705); Gilmour, D. G.; Romero, C. H.; Okazaki, W. *Nature* 270(5632): 61-62; 1977.

Susceptibility to avian lymphoid leukosis infection was investigated in genetically resistant East Lansing line 6 subline (R) chicks and the genetically susceptible chicks from the F class of East Lansing inbred lines 15 subline 1 and 7 subline 2 (S). Recipient chicks were treated with three 4-mg doses of cyclophosphamide on days 0, 1, and 2 after hatching and injections of bursal lymphocytes from 10-day-old donors on day 3. The doses were 1.15×10^8 cells from susceptible donors but only 7×10^7 cells from resistant donors. Within 1 day all chicks were infected iv with $> 10^4$ tissue culture infective doses of avian leukosis virus and vaccinated against Marek disease by im inoculation with approx 2,000 plaque-forming units of turkey herpesvirus vaccine. Regardless of recipient genotype, lymphoid leukosis occurred only in chicks receiving bursal cells from susceptible donors. Successful B-cell functional reconstitution with bursal cells was achieved in almost all syngeneic transfers. Similar results were obtained in experiments in which susceptible chicks were reconstituted with syngeneic bursal cells. It is concluded that resistance to lymphoid leukosis of line 6 subline 1 chickens resides in the bursal cells and not in other cells of the immune system. (2 refs.)

- 77-6468 **B Lymphocyte Colony-Forming Cells in the SJL/J Mouse Thymus.** (Eng) Claesson, M. F. (Walter and Eliza Hall Inst., Royal Melbourne Hosp., P.O. 3050, Victoria, Australia); Metcalf, D. *J Immunol* 118(4): 1208-1212; 1977.

Aging SJL/J mice accumulated increasing numbers of B lymphocyte colony forming cells in the thymus from the third mo of life onward. B-lymphocyte infiltration of the thymus apparently preceded the development of spontaneous reticulum cell tumors which appeared in some mice after 6 mo of age, suggesting that the thymus played a role in tumorigenesis. (11 refs.)

- 77-6469 **Inhibition of Lymphocyte Proliferation by Factors Produced by *Schistosoma mansoni*.** (Eng)

Dessaint, J. P. (Laboratoire d'Immunologie et de Biologie Parasitaire, U.E.R de Medecine, Lille, France); Camus, D.; Fischer, E.; Capron, A. *Eur J Immunol* 7(9): 624-629; 1977.

Proliferation of T and B cells was inhibited by the addition of the incubation product of *Schistosoma mansoni* and the cell-free supernatant of schistosoma culture to CBA mice and Fischer/Ico rat spleen cells in vitro at the beginning of culture. The inhibitor appeared to be heat resistant and dialyzable, and had a mol wt of 500 to 1,000. (24 refs.)

77-6470 Lymphocyte Migration into Cell-mediated Immune Lesions Is Inhibited by Trypsin. (Eng.)

Rannie, G. H. (Dept. Pathology, Univ. Manchester Medical Sch., Manchester, England); Smith, M. E.; Ford, W. L. *Nature* 267(5611): 520-522; 1977.

Lymphocytes obtained by thoracic duct cannulation of inbred AS or (PVG/c x DA)F₁ rats were radiolabeled in vitro with ⁵¹Cr-sodium chromate (10 µCi/ml) and treated with trypsin (0.02 mg/ml) for 10 min. Trypsinized cells were injected iv into separate syngeneic recipients that were killed at 0.5, 2, and 24 hr after injection. Two series of experiments were performed involving recipients with either (1) contact sensitivity lesions induced by painting an area of ventral abdominal skin with 0.1 ml of 5% dinitrochlorobenzene (DNCB) or (2) adjuvant granulomas produced by id injection 21 days previously of 0.1 ml of Freund's complete adjuvant. Few lymphocytes (1%-2%) entered the lymph nodes and skin or the granuloma as a result of DNCB challenge, whereas migration of lymphocytes into the spleen, liver, and normal skin was not impaired. Thus, two mechanisms of selective migration may exist: the first, which is trypsin-resistant, may operate in the spleen and nonlymphoid tissues and the second, which is trypsin-sensitive, may operate in the lymph nodes and sites of cell-mediated immune lesions. (13 refs.)

77-6471 Lymphocytes Bearing Receptors for Both Sheep Erythrocytes and Complement in Patients with

Neoplastic and Non-neoplastic Diseases. (Eng) Gajl-Peczalska, K. J. (Dept. Lab. Medicine and Pathology, Univ. Minnesota, Minneapolis, MN 55455); Chartrand, S.; Bloomfield, C. D.; Corte, J.; Coccia, P. F.; Nesbit, M. E.; Kersey, J. H. *Clin Immunol Immunopathol* 8(2): 292-299; 1977.

A combined rosette assay using uncoated sheep erythrocytes (sE) and chicken erythrocytes coated with antibody and complement (cEAC') was developed to identify lymphocytes with receptors for both sE and complement (C'). Blood samples from 100 healthy volunteers gave a mean value of 0.8% for double-receptor lymphocytes. Malignant lymphoid cells from four patients formed both sE and cEAC' rosettes. Of these patients, two were children with mediastinal masses whose

double rosette-forming cells lacked other surface markers. The other two patients were adults with chronic lymphocytic leukemia, and their cells also carried surface immunoglobulin and Fc receptors. Of 184 patients with lymphoid malignancy, 4 demonstrated an increased percentage (7%-11%) of non-malignant lymphocytes forming double rosettes. There was no increase of double-receptor lymphocytes in the circulating lymphocytes from 103 patients with nonlymphoid malignancies. An increase of double-receptor lymphocytes was rare in the 183 patients with nonneoplastic disease and was only found in children. Double-receptor lymphocytes may represent an immature or stem cell lymphocyte subset. The appearance of these cells in children with nonneoplastic diseases suggests that children may have an increased number of double-receptor lymphocytes in the basal state and/or under the stress of disease. (24 refs.)

77-6472 Rosette Formation in Chicks: With Special Reference to QRBC-Rosettes. (Eng) Sato, K.

(Dept. Animal Physiology, Nagoya Univ., Nagoya, 464, Japan); Itoh, M. *Adv Exp Med Biol* 88: 121-133; 1977.

Rosette formation was investigated in Anthony and Hy-line strain chicks by using RBC from the wild-type plumage stock of Japanese quail (*Coturnix coturnix japonica*). To clarify the interaction between lymphocytes and QRBC, several rabbit antisera and the following agents were used: cytochalasin B, 2.5-20.0 µg; vinblastine sulfate, 10⁻³-10⁻⁴ M; colchitin, 10⁻⁴-10⁻³ M; pronase, 200-400 µg; trypsin, 200 µg; neuraminidase, 0.1 unit; and hyaluronidase, 50 units. The distribution of loosely and firmly bound rosette-forming cells (L-RFC and F-RFC) in the peripheral blood and thymus was different from that in the bone marrow, spleen, and bursa of Fabricius. This suggests that F-RFC and L-RFC represent separate subpopulations of lymphoid cells in chicks. The age of the chicks influenced the number of QRBC rosettes, indicating that L-RFC and F-RFC are interrelated in the maturation of the lymphoid system. Differences in the breed or strain of the birds also affected rosette formation. Cytochalasin B completely inhibited rosette formation; pronase and trypsin produced > 50% inhibition; neuraminidase and anti-light chain and anti-heavy (µ) chain sera, > 20%; colchitin and anti-heavy (γ) chain sera, < 20%; and vinblastine sulfate and hyaluronidase had no effect. L-RFC and F-RFC were inhibited equally by these agents. The ontogenetic developments of both RFC subpopulations suggest the presence of their interrelation in the maturation of the chick lymphoid system. (11 refs.)

77-6473 Immunological Defects in Healthy Twin Siblings to Patients with Hodgkin's Disease.

(Eng) Bjorkholm, M. (Dept. Medicine, Serafimerlasarettet, S-112 83 Stockholm, Sweden); Holm, G.; de Faire, U.; Mellstedt, H. *Scand J Haematol* 19(4): 396-404; 1977.

Immunocompetence was studied in six healthy twins whose monozygotic or dizygotic same-sex twin partner had died from Hodgkin's disease. Concanavalin A-induced lymphocyte DNA synthesis was markedly reduced at three different concentrations in all twins compared with age-matched healthy controls. The lymphocyte response to pokeweed mitogen and phytohemagglutinin was also impaired. Lymphocyte DNA synthesis induced by a purified protein derivative of tuberculin was low in three twins and correlated well with their delayed skin hypersensitivity to the antigen. One twin was completely anergic to three different skin antigens. The mean total blood lymphocyte count did not differ from that of controls. There was no change in T- or B-lymphocyte subpopulations. The presence of a functional lymphocyte deficiency in all twins strongly suggests that the immunodeficiency in Hodgkin's disease is partly caused by genetic and/or environmental factors. (35 refs.)

- 77-6474 **Common Clonal Origin of Lymphoplasmacytic Proliferation and Immunoblastic Lymphoma in Intestinal α -Chain Disease (Letter to Editor).** (Eng) Pangalis, G. A. (Dept. Anatomic Pathology, City of Hope Natl. Medical Center, Duarte, CA 91010); Rappaport, H. *Lancet* 2(8043): 880; 1977.

A search was made for intracellular immunoglobulin in tissue sections from both benign-appearing lymphoplasmacytic lesions and immunoblastic lymphomas in three patients with α -chain disease. A high percentage of plasma cells and plasmacytoid lymphocytes in the lymphoplasmacytic lesions and neoplastic cells of the immunoblastic lymphomas was positive for α -chains, but the adjacent tissue was negative for γ , μ , κ , and λ chains. These findings suggest a common clonal origin for the lymphoplasmacytic proliferation and the lymphoma in intestinal α -chain disease. (10 refs.)

- 77-6475 **Binding Studies on Anti-fructofuranan Mouse Myeloma Immunoglobulins A47N, A4, U61, and E109.** (Eng.) Streefkerk, D. G. (Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, NIH, Bethesda, MD 20014); Glaudemans, C. P. *Biochemistry* 16(17): 3760-3765; 1977.

The binding of inulin and a series of oligosaccharides derived from inulin with mouse myeloma immunoglobulins A4, A47N, U61, and E109 was studied by ligand-altered fluorescence. The combining site of these immunoglobulins showed the highest complementarity for a trifructofuranosyl sequence (A4 and A47N) and a tetrafructofuranosyl sequence (U61 and E109). (32 refs.)

- 77-6476 **Temperature-dependent Changes of Myeloma Immunoglobulin G (K) IVA, Bence-Jones Pro-**

tein (K-Type) IVA and Its Fragments. (Eng) Zav'yalov, V. P. (Dept. Biochemistry, Crimean Medical Inst., Simferopol USSR); Demchenko, A. P.; Suchomudrenko, A. G. Troitsky, G. V. *Biochim Biophys Acta* 491(1): 7-15; 1977.

Thermal perturbation difference spectroscopy and circular dichroism showed that IgG(K) IVA and Bence-Jones protein (K-type) IVA were capable of fully reversible structural changes at temperatures ranging from 25 to 35 C. At higher temperatures, the changes were accompanied by screening of a significant part of exposed tyrosine residues. Changes of IgG occur in its Fab fragments, those of Bence-Jones protein in its variable (V-L) domains. These temperature-sensitive changes may be due to an alteration of amino acid side chains on the "sides" of the immunoglobulin cavities between variable domains. (28 refs.)

- 77-6477 **Idiotypic Determinants on the Surface Immunoglobulin of Neoplastic Lymphocytes: A Therapeutic Target.** (Eng.) Stevenson, G. T. (Tenovus Res. Lab. Southampton Medical Sch., General Hosp., Southampton, England); Elliott, E. V.; Stevenson, F. K. *Fed Proc* 36(9): 2268-2271; 1977.

Antibodies raised against idiotypic determinants on the surface immunoglobulin (Ig) of neoplastic lymphocytes were used in therapeutic trials. Since idiotypic determinants of surface Ig can occur on neoplastic lymphocytes, these determinants represent a unique class of tumor-specific antigen. Antibodies against the complete surface IgM, designated anti-I ($\mu\lambda$), were prepared by cleaving and solubilizing the Fab μ fragment by treating L₂C leukemic cells with papain, purifying Fab μ by immunosorption to modified Sephadex G-2B, and injecting the Fab μ -Sephadex complex with adjuvant into guinea pigs or sheep. Antibodies were also prepared against the λ chain of IgM, called anti-Id (λ). Anti-Id effectively inhibited the cellular migration of motile tumor cells (e.g., L₂C) and caused cytotoxic reactions by activation of complement or of K cells. Xenogeneic anti-Id ($\mu\lambda$) and anti-Id (λ) significantly prolonged the survival of L₂C-bearing guinea pigs. (27 refs.)

- 77-6478 **Characterization of Syngeneic Anti-idiotypic Antibody Against the Idiotypic of BALB/c Myeloma Protein J558.** (Eng) Schuler, W. (Universitat Konstanz, Fachbereich Biologie, D-7750, Konstanz, W. Germany); Weiler, E.; Kolb, H. *Eur J Immunol* 7(9): 649-654; 1977.

The antibody response of BALB/c mice against the myeloma protein J558 was investigated, and the number of anti-idiotypic molecular species was determined. Immunization of the mice resulted in approx 70% of the mice exhibiting anti-J558 activity. Inhibition studies with other BALB/c myeloma sera indicated that only the native J558 myeloma

era were effective; thus, the syngeneic antisera are highly specific for the idiotype of J558. Sera from immunized C57BL and CB20 mice did not inhibit the reaction. In the presence of 10^{-2} nigerotriose, the hemagglutination reaction by syngeneic anti-idiotype serum was completely inhibited. Nigerose inhibition was almost complete at the same concentration; trehalose had no effect. A comparison of syngeneic antisera from several individual mice indicated that the isoelectric focusing patterns of each mouse were different. When cells from immunized mice were injected into lethally irradiated mice, the anti-idiotypic populations were boosted. Further studies indicated that the recipients expressed an almost comprehensive sample of the total set of donor clones. The heterogeneous pattern of isoelectric focusing could be due to V- as well as C-region heterogeneity. A study of clone repetition indicated that the anti-idiotypic repertoire of the BALB/c strain directed against J558 protein is at least 100 isotypes. (31 refs.)

77-6479 **Alteration of Cell-Surface Antigenicity of the Mouse Plasmacytoma. II. Lack of Correlation between Synthesis of Myeloma Protein and Alteration of Surface Antigen.** (Eng) Ohno, S. (Dept. Molecular Immunology, Cancer Res. Inst., Kanazawa Univ., 13-1 Takarauchi, Kanazawa, Japan); Natsu-ume-Sakai, S.; Migita, S. *Natl Cancer Inst* 58(2): 229-237; 1977.

The correlation between changes of immunoglobulin (Ig) synthesis and surface antigenicity was analyzed by cytotoxicity and quantitative antibody-absorption tests of Ig-producing and nonproducing mouse plasmacytomas. IgA-synthesizing BALB/c plasmacytoma 58-8 and its non-IgA-synthesizing variant were killed with rabbit anti-58-8 plasmacytoma cell antiserum, C3H/He anti-BALB/c spleen cell antiserum, and C57BL/6 x DBA/2F₁ anti-BALB/c plasmacytoma cell TOPC-31C antiserum plus complement, but only when the cells were pretreated with pronase. Quantitative absorption tests showed that, compared with the producer tumor, the nonproducer had the same amount of 58-8 plasmacytoma antigen and PC1 antigen, and a greater amount of M-2 antigen. C3H mouse plasmacytoma X5563, which has an M component of IgG₂a, was also analyzed. Nonproducer X5563 had a greater amount of H-2k antigen and a smaller amount of the plasmacytoma antigen of X5563 than did producer X5563. No PC.1 antigen was detected on the surfaces of the producer and nonproducer cells. It is concluded that PC.1 antigen is not always a membrane component necessary for synthesis and that the amount of H-2 antigens is not always reduced in non-Ig-synthesizing myeloma cells. (22 refs.)

77-6480 **Galactosyltransferase Activity in Metastasizing and Nonmetastasizing Rat Mammary Carcinomas and Its Possible Relationship with Tumor Cell Surface Antigen Shedding.** (Eng) Chatterjee, S. K. (Dept. Pathology, Roswell Park Memorial Inst., New York State Dept.

Health, Buffalo, NY 14263); Kim, U. *J Natl Cancer Inst* 58(2): 273-280; 1977.

Galactosyltransferase (GT) levels were compared in five spontaneously metastasizing and three nonmetastasizing rat mammary tumors. GT levels in the presence of both endogenous and exogenous acceptors were higher in the metastasizing tumors than in the nonmetastasizing ones. This difference did not seem to be due to any variation in levels of degrading enzymes such as pyrophosphatase or β -galactosidase in the tumors. No differences in the properties of the enzyme in the two tumor groups were observed, and the affinity of their enzyme was similar for the substrate uridine diphosphate-galactose as well as the agalacto-fetuin acceptor. Most of the enzyme activity (60%-70%) was found in the microsomal fraction. When GT was assayed in purified plasma membrane fractions, 70% was associated with the plasma membrane vesicles. The number of galactose acceptor sites on the plasma membranes increased in proportion to metastasizing capacity, indicating the presence of larger numbers of incomplete glycopeptides on their cell surfaces. The higher GT activity in the metastasizing tumors may indicate that the greater turnover of the membrane glycoprotein components is due to the steady shedding of surface antigens into the systemic circulation, rather than to a differential growth rate of tumor cells, because these two tumor groups were matched according to their growth rates. (42 refs.)

77-6481 **Avian Retrovirus-induced Surface Antigens and Their Cross-reactivity with Chemically-transformed Cells and Primary Embryonic Cells of Japanese Quails.** (Eng) Hayami, M. (Institut für Virologie, Fachbereich Humanmedizin der Justus-Liebig Universität Gießen, Frankfurter Strasse 107, 63 Gießen, W. Germany); Ignjatovic, J.; Bauer, H. *Int J Cancer* 20(5): 729-737; 1977.

Cell-surface antigenic components expressed on Japanese quail cells infected by various avian retroviruses were identified by cell-mediated cytotoxicity. Spleen cells from quail bearing avian sarcoma virus (ASV) tumors and from quail infected with Rous-associated virus (RAV-5) exerted a cytotoxic effect against embryonic quail cells transformed or productively infected by viruses of the same subgroup; uninfected sister cells were not destroyed. Studies in which ASV-transformed and avian leukosis virus (ALV)-infected cells were reacted with effector cells immunized by ALV of different subgroups indicated that the cytotoxic effects of ALV-infected animals were mostly subgroup-specific and independent of whether the cells were transformed or productively infected. Thus, the target antigen complex is thought to be expressed on the cytoplasmic membrane of the transformed cells. Quail 3-methylcholanthrene-transformed tumor cells, which show a transformation phenotype similar to that of ASV-transformed cells, but are free of detectable endogenous and exogenous retrovirus, were also destroyed by spleen cells from ASV tumor-bearing animals. This indicates that it is unlikely that a viral structural antigen is in-

volved in the reaction. The cytotoxic effect of the effector cells on primary embryo cells disappeared after the second passage. (25 refs.)

- 77-6482 **Role of the Major Histocompatibility Locus in Resistance of Chickens to Marek's Disease (Meeting Abstract).** (Eng) Gavora, J. S. (Animal Res. Inst., Agriculture Canada, Ottawa, Ontario, Canada); Longenecker, B. M.; Pazderka, F.; Spencer, J. L. *Can J Genet Cytol* 19(3): 573; 1977. (1 ref.)

- 77-6483 **Role of Tumor Antigen in Vaccine Protection in Marek's Disease.** (Eng) Sharma, J. M. (U. S. Dept. Agriculture, Agricultural Res. Service, Regional Poultry Res. Lab., 3606 E. Mount Hope Road, East Lansing, MI 48823). *Adv Exp Med Biol* 88: 345-353; 1977.

Chickens that were the F₁ progeny of a cross between inbred lines 15 and 7 were inoculated intraabdominally with 2×10^4 plaque-forming units (PFU) of the Fc 126 isolate of herpes-virus of turkey (HVT) or with 10^4 PFU of clone 111S of the JM isolate of Marek's disease virus (MDV). After 7 and 8 days, samples of inoculated and uninoculated birds were examined for lesions in the peripheral nerves and gonads and for a cell-mediated cytotoxic response to MD tumor-associated surface antigen (MATSA) in an in vitro cytotoxicity assay. Chickens vaccinated with HVT developed lymphoproliferative lesions in the peripheral nerves and gonads and had a cell-mediated immune response to MATSA. In this vaccination system, the host apparently develops MATSA immunity in response to transformation initiated by MDV. This immune response is probably the greatest factor in the vaccine protection of chickens against the clinical manifestations of MD. (24 refs.)

- 77-6484 **Expression of MuLV GP71-like Antigen in Normal Mouse Spleen Cells Induced by Antigenic Stimulation.** (Eng) Wecker, E. (Institut für Virologie und Immunobiologie der Universität Würzburg, Versbacher Landstrasse 7, D-8700 Würzburg, W. Germany); Schimpl, A.; Hunig, T. *Nature* 269(5629): 598-600; 1977.

Both T- and B-lymphocytes of C57Bl/6 mice displayed Friend leukemia virus (FLV) glycoprotein 71 (gp71)-like surface antigens when antigenically stimulated by dinitrophenyl-KLH. Furthermore, when DNP-KLH-stimulated mouse spleen cells were treated with goat anti-FLV gp71 antiserum, the secondary in vitro immune response was practically abrogated. This suggests that antigen-specific immune responses can be suppressed by applying the appropriate antisera against oncoviral antigens such as gp71. (17 refs.)

- 77-6485 **Detection of Carcinoembryonic-like Antigen on Melanoma Cells by Leucocyte-Dependent-Antibody Assays.** (Eng) Morgan, G. (Kanematsu Memorial Inst., Sydney Hosp., Sydney, N.S.W., 2000, Australia); McCarthy, W. H.; Hersey, P. *Br J Cancer* 36(4): 446-452; 1977.

Carcinoembryonic antigen (CEA)-like antigens on melanoma cells were examined using a rabbit antiserum against CEA in a leukocyte-dependent cytotoxic-antibody assay (LDA). CEA-specific reactivity of the antiserum was removed after absorption on CEA affinity columns. LDA activity to CEA was also found in sera from a woman in her third trimester. No CEA LDA activity was found in several melanoma sera. CEA may be important in tumor rejection; monitoring of its levels could be valuable in measuring disease activity. (23 refs.)

- 77-6486 **Two Mechanisms of Migration Inhibition Factor Induction by Tumour Antigens.** (Eng) Landolfo, S. (Lab. Immunodiagnosis, NCI, NIH, Bethesda, MD 20014); Herberman, R. B.; Holden, H. T. *Nature* 270(5632): 62-64; 1977.

Migration inhibition factor (MIF) production was investigated in immune spleen cells from C57BL/6N mice 12 to 14 days after they were inoculated with a regressor strain of Moloney murine sarcoma virus. When soluble tumor-associated antigens were used, the immune T lymphocytes required macrophages for MIF production and, in addition, only histocompatible macrophages could assist immune T lymphocytes in the release of MIF. When soluble tumor extracts were used as the source of antigen, gene products of the H-2 complex regulated the macrophage-immune lymphocyte interaction for MIF release. When intact tumor cells were used, macrophages were not required. Since allogeneic as well as syngeneic tumor cells could activate MIF release from immune lymphocytes, direct lymphocyte-tumor cell interaction for MIF release was not under H-2 restriction. It is suggested that there are at least two pathways for MIF production, reflecting two distinct subpopulations of T lymphocytes or the activation of T lymphocytes at different stages of differentiation. (16 refs.)

- 77-6487 **HLA-SD Antigens in Cervical Cancer and Recurrent Herpes Genitalis (Report).** (Ger.) Dostal, V. (Institut für Krebsforschung, Austria); Mayr, W. R. *Oesterr Z Onkol* 3(5/6): 119-121; 1977.

The occurrence of 36 histocompatibility antigens in 42 patients with cervical cancer, 36 women with recurrent Herpes genitalis and 450 healthy controls was evaluated. An increase in the frequency of BW 15 in the cancer patients was the only significant difference between the groups. In spite of their increased rash of cervical carcinoma, the patients with recurrent Herpes genitalis showed no significant difference in antigen frequencies compared with the other two groups. (6 refs.)

7-6488 **Chromatographic and Electrophoretic Analysis of an Antigen in Hodgkin's Disease Tissue Cultures.** (Eng) Long, J. C. (Dept. Pathology, Immunopathology-Cox 5, Massachusetts General Hosp., Boston, MA 02114); Aisenberg, A. C.; Zamecnik, P. C. *J Natl Cancer Inst* 8(2): 223-227; 1977.

An antigen in tissue cultures derived from Hodgkin's disease (HD) tumors was characterized by polyacrylamide gel electrophoresis (PAGE), Sephadex column chromatography, and indirect radioiodine-labeled antibody techniques. Fourteen long-term, serially passaged monolayer cultures prepared from tumor nodules of HD in the spleen were studied. Eleven cultures were used as controls: eight normal splenectomy specimens and one each from human fetal spleen, thymus, and lung. Cell-free medium from HD and normal cultures was centrifuged, sedimented in a discontinuous sucrose gradient, and fractionated by PAGE and Sephadex column chromatography. A component was observed in medium from HD cultures that was not detected in the normal cultures. Rabbit antiserum against this component reacted by radioiodine-labeled antibody assay with an antigen on the surface of cells from HD cultures that was present in very small amounts, or in a cryptic state, on normal cells. The antigen has not been demonstrable in noncultured HD tumor cells. It is suggested that the antigen may be a normal cellular constituent present in greatly increased amounts in HD cultures, a dedifferentiated tumor neoantigen, or a viral component whose expression requires prolonged replication of cells in culture. (28 refs.)

7-6489 **A Surface Antigen Associated with Hodgkin's Disease: Brief Communication.** (Eng) Favre, R. Groupe d'Hematologie, Unite de Recherches de Cancerologie Experimentale U-119, Institut National de la Sante et de Recherche Medicale, 27, Bd Lei Roure, 13009 Marseille, France); Carcassonne, Y.; Meyer, G. *J Natl Cancer Inst* 9(6): 1727-1730; 1977.

Lymph node cells from a patient with Hodgkin's disease were injected into a rabbit and the resultant antisera were tested on 24 lymph node and 3 spleen specimens from patients with all stages of Hodgkin's disease. Twenty-five of the 27 reactions were positive; benign and malignant non-Hodgkin's disease lesions did not react. The nature of the antigen and the type of cells bearing it are unknown. (21 refs.)

7-6490 **Biological and Biochemical Properties of Nonidet P40-solubilized and Partially Purified Tumor-specific Antigens of the Transplantation Type from Plasma Membranes of a Methylcholanthrene-induced Sarcoma.** (Eng) Natori, T. (Lab. Cell Biology, NCI, NIH, Bethesda, MD 20014); Law, L. W.; Appella, E. *Cancer Res* 37(9): 3406-3413; 1977.

Tumor-specific transplantation antigen (TSTA) was solubilized from cell membranes of a methylcholanthrene-induced sarcoma (sarcoma Meth-A) with nonionic detergent Nonidet

P40. Soluble TSTA was partially characterized by chromatographic separation and electrophoresis. The antigen responsible for tumor rejection activity had a mol wt of approx 70,000 daltons in the presence of detergent and an electrophoretic mobility of α -globulin. TSTA was well separated from mouse histocompatibility antigen H-2 by lectin affinity chromatography. The antigen purified by a sequence of procedures, including gel filtration, lectin affinity chromatography, column electrophoresis, and rechromatography on agarose, showed only three major bands on polyacrylamide gel electrophoresis. TSTA was specific for sarcoma Meth-A. (28 refs.)

77-6491 **Common Tumor-associated Transplantation Alloantigen Detected on a Proportion of Lung Tumors Induced Transplacentally in Several Strains of Mice.** (Eng) Martin, W. J. (Div. Virology, Bureau Biologics, Food and Drug Admin., Bethesda, MD 20014); Gipson, T. G.; Conliffe, M.; Friedman, R. J.; Dove, L.; Rice, J. M. *Transplantation* 24(4): 294-296; 1977.

Lung tumors induced in C57BL/6N and DBA/2N mice by the transplacental administration of 1-ethyl-1-nitrosourea were tested for their ability to induce radioresistant syngeneic immunity against challenge with a C3Hf/HeN lung tumor (tumor 85) that expresses the A/HeN-associated alloantigen. In these experiments, groups of (C3Hf/HeN x C57BL/6N) F_1 and C3Hf/HeN mice were inoculated with fragments of the C57BL/6N tumors, and (C3Hf/HeN x DBA/2N) F_1 and C3Hf/HeN mice were inoculated with fragments of the DBA/2N tumors. Three tumors of C57BL/6N origin and two of DBA/2N origin showed strong cross-immunity against tumor 85. None of the five tumors induced detectable radioresistant anti-85 immunity in (C3Hf/HeN x A/HeN) F_1 recipients, which indicated that they probably expressed the strain A-associated alloantigen. (6 refs.)

77-6492 **Demonstration of Cross-reacting Tumor Rejection Antigens in Chemically Induced Respiratory Tract Carcinomas in Rats.** (Eng) Jamasbi, R. J. (Univ. Tennessee-Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN 37830); Nettesheim, P. *Cancer Res* 37(11): 4059-4063; 1977.

Experiments were performed to determine whether benzo(a)-pyrene-, 3-methylcholanthrene, and 7,12-dimethylbenz(a)anthracene-induced rat respiratory tract carcinomas, which possess considerable immunogenicity, contain cross-reacting antigens. In vivo studies with Fischer 344 rats showed that effective cross-protection was induced with 4/5 respiratory tract cancers studied, suggesting that these tumors have common tumor-rejection antigens. In vitro cytotoxicity studies with sera from tumor-immune hosts showed cross-reactivity among three of the carcinomas tested. Data are presented that suggest that the antigens are not related to embryonic antigens or to RNA viruses. (22 refs.)

- 77-6493 **Common Transplantation Antigens on Methylcholanthrene-induced Murine Sarcomas Detected by Three Assays of Tumor Rejection.** (Eng) Leffell, M. S. (Clinical Microbiology Lab., Dept. Hosp. Labs., North Carolina Memorial Hosp., Chapel Hill, NC 21514); Coggin, J. H. *Cancer Res* 37(11): 4112-4119; 1977.

A substantial cross-reaction was demonstrated between two 3-methylcholanthrene (3-MC)-induced sarcomas (1315 and 1321) in BALB/c mice. These tumors had been reported to carry individually specific transplantation antigens. The cross-reaction was shown to depend on method as well as prior immunization secondary challenge dose. Specificity between the surface antigens on the 1315 and 1321 sarcomas was demonstrated only in experiments in which initial immunization was achieved by excision of progressively growing tumors, followed by rechallenge with either the homologous or reciprocal tumor line. In these experiments, cross-protection was obtained at low doses of secondary challenge cells (1×10^4), but specificity was observed at high secondary challenge levels (5×10^5). In a series of transplantation studies, mice were preimmunized with serial doses of irradiated tumor cells and then challenged with live tumor cells. In all cases, significant (70%-100%) cross-protection between the two sarcoma lines occurred. The cross-reaction appeared to be specific for the chemically induced tumors, since preimmunization against the 1315 or 1321 sarcoma gave no significant protection against challenge with a syngeneic line of simian virus 40-induced sarcoma cells. Cross-protection was also confirmed when different sublines of high and low in vivo passages were compared. The results of the direct challenge experiments were confirmed by passive transfer of live tumor cell challenges mixed with peritoneal exudate cells from immunized animals to syngeneic, unimmunized recipients. (24 refs.)

- 77-6494 **A Distinctive Antigen Present in Liver Carcinomas Induced by 3'-Methyl-p-dimethylaminoazobenzene.** (Eng) Carruthers, C. (Dept. Carcinogenesis, Orchard Park Labs., Roswell Park Memorial Inst., Buffalo, NY 14263); Bauml, A.; Neilson, A. *Oncology* 34(2): 47-51; 1977.

The distribution of a distinctive antigen present in liver carcinomas induced in Fischer rats by the administration of 3'-methyl-p-dimethylaminoazobenzene (3'-Me-DAB) was investigated using immunofluorescence, immunoelectrophoresis, and immunodiffusion. Antisera were raised against the carcinoma supernatant fraction (SF) obtained by differential centrifugation of a sucrose homogenate of a mixture of cholangiocarcinomas and hepatocellular carcinomas. The antisera gave specific fluorescence in both 3'-Me-DAB induced tumors. The anticarcinoma SF antisera did not show specific fluorescence staining in 3'-Me-DAB treated liver cells in the early and late stages of carcinogenesis or in the kidney, spleen, skeletal muscle, liver, and skin of normal rats. The carcinoma-distinctive antigen does not appear to be the carcinoembryonic antigen-fetoprotein (AFP), because AFP appeared early in the sera of rats after 3'-Me-DAB, but the

carcinoma-distinctive antigen was found 3-6 mo after sc administration of the carcinogen. Antisera raised against the preneoplastic antigen (PN) gave specific fluorescence in the cytoplasm of hepatomas but not in the nuclei, but antisera raised against the carcinoma SF antigen gave both specific cytoplasmic and intranuclear fluorescence in both hepatocellular carcinomas and cholangiocarcinomas. This indicates that the carcinoma-distinctive antigen is not the same as the PN antigen. (18 refs.)

- 77-6495 **Are Endogenous C-Type Viruses Involved in the Immune System?** (Eng) Moroni, C. (Friedrich Miescher-Institut, Post Office Box 273, CH-4002 Basel, Switzerland); Schumann, G. *Nature* 269(5629): 600-601; 1977.

The effect of antisera against xenotropic endogenous C-type viruses on the humoral immune response of BALB/c mice was determined. In vivo and in vitro experiments revealed that these sera were immunosuppressive. This may be a result of complement-dependent cytotoxicity directed against lymphocytes participating in antigenic responses, the close proximity of the viral antigen to a membrane structure necessary for the immune response, or the requirement of viral antigen itself on the membrane. (13 refs.)

- 77-6496 **Development and Regression of Shope Papillomas Induced in Newborn Domestic Rabbits.** (Eng) Seto, A. (Dept. Microbiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan); Notake, K. *Proc Soc Exp Biol Med* 156(1): 64-67; 1977.

The role of the immune system was investigated in the regression of papillomas induced in newborn rabbits by the injection of Shope papilloma virus. Regression was evident in only 7/55 animals (13%), but antibodies were induced in all. Skin reactions were observed in some rabbits in both persisting and regressing groups. It was concluded that there is no correlation between regression and immune response. (13 refs.)

See also:

- *(Rev.): 77-6017, 77-6092, 77-6093, 77-6094, 77-6095, 77-6096, 77-6097, 77-6098, 77-6099, 77-6100, 77-6102, 77-6103.
 *(Chem.): 77-6197, 77-6215, 77-6230, 77-6289.
 *(Viral): 77-6312, 77-6324, 77-6325, 77-6327, 77-6328, 77-6329, 77-6331, 77-6332, 77-6341, 77-6346, 77-6349, 77-6352, 77-6356, 77-6361, 77-6371, 77-6375, 77-6383, 77-6397, 77-6401, 77-6409, 77-6410, 77-6411, 77-6412, 77-6413, 77-6426, 77-6427, 77-6428, 77-6429.
 *(Path.): 77-6510, 77-6557, 77-6560, 77-6567.

PATHOGENESIS

- 77-6497 **Light-Microscopic Morphology of Cell Types Cultured During Preneoplasia from Foreign Body-reactive Tissues and Films.** (Eng.) Johnson, K. H. (Dept. Veterinary Pathobiology, Coll. Veterinary Medicine, Univ. Minnesota, St. Paul, MN 55108); Buoen, L. C.; Brand, I.; Brand, K. G. *Cancer Res* 37(9): 3228-3237; 1977.

Light microscopy was used to characterize and morphologically identify four cell types isolated in vitro from preneoplastic foreign body (FB)-reactive tissues and films. Type I cells were predominantly round to spindle or fusiform in shape, but there were a few stellate (tripolar) shapes. Numerous basophilic cytoplasmic granules and occasional vacuoles were evident. These cells were designated macrophage-like cells. Type II cells, considered fibroblast-like, were most often large, irregularly stellate (multipolar) cells with a few strap-like (bipolar) forms. Type III cells were characteristically very narrow and fusiform (bipolar), with a few stellate cells. Type IV cells were polygonal to stellate in shape, with quadrilateral (kitelike) shapes common; they had other characteristics that were consistent with their being endothelial cells. Types I and II cells predominated in primary cultures and early passages (1 and 2) of cells derived from FB-reactive capsule tissue. The appearance of small numbers of Type III cells in early passages coincided with the deterioration of Type III cell populations and preceded the appearance of Type IV cells. Type IV cells had a growth advantage over the other types, resulting in culture composed only of Type IV cells after three passages. Type IV cells were aneuploid and could produce homologous sarcomas when injected as a suspension into compatible hybrid recipient mice. The relationship of Type IV cell, the presumptive progenitor cell type in FB tumorigenesis, to the other cell types is discussed. (19 refs.)

- 77-6498 **Ultrastructure of Ewing's Tumour.** (Eng.) Povyšil, C. (Second Dept. Pathology, Faculty General Medicine, Charles' Univ., Prague 2, U nemocnice 4, Czechoslovakia); Matejovsky, Z. *Virchows Arch [Pathol Anat]* 374(4): 303-316; 1977.

Tumor tissue from 10 patients with Ewing's tumor of the bones was examined electron microscopically and histoenzymologically. All of the tumors were composed of polygonal cells. The cytoplasm of these cells was rather scanty and poor in organelles, but it did contain large conspicuous aggregates of glycogen particles. The presence of primitive desmosomes or so-called atypical junction complexes was noted. In addition to these light cells, a few dark cells with long narrow processes were seen. Cell-membrane-bound alkaline phosphatase activity was demonstrated in all the tumors examined

except two, which were from patients who had undergone long-term cytotoxic treatment. The histogenesis of Ewing's tumor remains uncertain, but this study supports a hemangiogenic origin. The differentiation of Ewing's tumor from neuroblastoma and malignant lymphomas is also discussed. (21 refs.)

- 77-6499 **Electron Microscopic Study of Signet-Ring Cells in Diffuse Carcinoma of the Human Stomach.** (Eng.) Yamashiro, K. (Lab. Pathology, Aichi Cancer Center, Res. Inst., Chikusa-ku, Nagoya 464, Japan); Suzuki, H.; Nagayo, T. *Virchows Arch [Pathol Anat]* 374(4): 275-284; 1977.

A light and electron microscopy study of the signet ring cells in diffuse type gastric carcinoma led to their classification into types A, B, and C. Type A cells had rounded or elliptical central nuclei, abundant cell organelles, and small, high, electron-dense mucous granules. Type B cells had elliptical eccentric nuclei, decreased organelles, and medium-sized mucous granules of medium electron density. Type C cells had crescent-shaped peripheral nuclei, few organelles, and large low-density mucous granules. The gradual transition of Type A cells to Type B and the subsequent change of Type B cells to Type C suggested successive stages in maturation. Type A and B were PAS-positive and were the predominant cells in diffuse carcinoma. Presumably, they are more active and more immature than the relatively infrequent alcian blue-positive Type C cells. It was concluded that intestinal type gastric carcinoma may arise from intestinal metaplastic epithelium, but that diffuse gastric carcinoma originates from nonmetaplastic gastric mucosa, with the appearance of Type A signet-ring cells as an initial malignant change. (14 refs.)

- 77-6500 **Gastrin Cells in Carcinoma of the Stomach. An Immunofluorescence Study with Special Reference to Cell Differentiation and Histogenesis.** (Jpn.) Nagata, T. (Second Dept. Pathology, Faculty Medicine, Kyushu Univ., Fukuoka, 812, Japan). *Fukuoka Acta Med* 68(7): 327-348; 1977.

The occurrence of immunofluorescent gastrin cells in 126 carcinomas and 4 adenomas of the stomach was investigated. Six of the 126 carcinomas had immunofluorescent gastrin cells; there were rarely > 10 such cells in a conventional field

of view. These cells were ovoid, their immunofluorescence was limited to the cytoplasm, and they were slightly larger than the cells of the noncancerous gastric mucosa. The nuclei were oval and hyperchromatic, but the nucleocytoplasmic ratio was smaller than that of malignant cells. The cells were concentrated in the mucosal layer of the tumor, usually in well-differentiated areas. Argrophil (58.9%) and argentaffin cells (19.8%) were also present. The excess of argrophil cells over the immunofluorescent cells indicated the presence of other hormone-secreting endocrine cells in the carcinoma. Six carcinomas in the pyloric antrum suggested that the carcinomas might have arisen from undifferentiated cells that were able to differentiate in various directions, including gastrin secretion. No immunofluorescent gastrin cells were found in the 4 adenomas and in 17 highly differentiated papillary adenocarcinomas; these tumors may have developed from the intestinalized mucosa of the stomach. (44 refs.)

77-6501 Specific Traits of Gastric Carcinoma Which Developed after Surgery for Peptic Ulcer.

(Rus.) Patiutko, Iu. I. (Dept. Oncology, First Moscow Medical Inst., Moscow, USSR); Mikhailov, E. A. *Klin Med (Mosk)* 55(7): 47-52; 1977.

The specific features of carcinoma of the gastric stump after gastric resection for peptic ulcer were analyzed in 64 patients with 67 tumors. Twenty-six patients had had gastric ulcer, 20 duodenal ulcer; the location of the ulcer could not be established in 21 cases. The interval from gastric resection to diagnosis of carcinoma was 6-40 yr (av 20.5 yr). The tumor was localized to the anastomosis in 18 cases, to the cardia in 22, and to the medial part in 11; it was generalized in 13 cases. Tumors that developed early after resection were often localized to the cardia, but those developing later affected different parts of the stomach at nearly the same frequency. Tumors that developed with delays of > 25 yr were predominantly localized to the anastomosis. Twenty-nine tumors were exophytic, 22 endophytic, and 16 were of the mixed type. The incidence of infiltrative and mixed forms in these patients was significantly higher than that in nonoperated controls, but no microscopic differences were found between the two groups. (17 refs.)

77-6502 Mucin Histochemistry in the Detection of Early Malignancy in the Colonic Epithelium. (Eng)

Filipe, M. I. (Dept. Histopathology, Westminster Medical Sch., Udall St., London, SW1P 2PP, England). *Adv Exp Med Biol* 89: 413-422; 1977.

Histochemical and biochemical studies of mucins in normal colonic mucosa and in precancerous and neoplastic conditions are reviewed. Sulfomucins were the main secretory products of the normal colonic mucosa, but sialomucins

predominated in transitional mucosa and in mucus-secreting adenocarcinomas. Although the changes in mucin composition were more marked in the mucosa adjacent to the carcinoma, they also occurred in sections of apparently healthy mucosa distant from the tumor. The possibility that these changes, together with ultrastructural changes, represent early events in carcinogenesis is discussed. This hypothesis is supported by data from studies of familial polyposis, ulcerative colitis, and experimental dimethylhydrazine-induced intestinal tumors. (16 refs.)

77-6503 Human Colon Adenocarcinoma Cells. II. Tumorigenic and Organoid Expression In Vivo and In Vitro. (Eng) Tom, B. H. (Lab. Surgical Immunology, Dept. Surgery and Physiology, Northwestern Univ., Medical Sch., Ward Memorial Building, 303 E. Chicago Ave., Chicago, IL 60611); Rutzky, L. P.; Oyasu, R.; Tomita, J. T.; Goldenberg, D. M.; Kahan, B. D. *J Natl Cancer Inst* 58(5): 1507-1512; 1977.

The neoplastic behavior of two human colon tumor cell lines, LS180, a nontrypsinized culture passaged 35 doublings, and LS174T, a trypsinized variant of LS180 passaged 95.6 doublings, was studied in vivo and in vitro. The LS174T cell line, recultured in vitro following passage through hamsters, displayed differences in its cell-doubling time and synthesis of carcinoembryonic antigen (CEA) when compared with cells grown solely in vitro. The animal-passaged cells more closely resembled the LS180 parent tumor line than the LS174T line. Analysis of lactate dehydrogenase isoenzymes indicated that the tumor cells recovered from the hamsters were free of xenogeneic host tissue. LS174T grafted to athymic (nude) mice grew as a mucinous adenocarcinoma microscopically resembling the original tumor. The altered growth potential of LS174T was also demonstrated on confluent feeder monolayers of normal cells and by uninhibited multiplication in vitro. The results suggest that, at least in this case, long-term LS174T cell cultures in vitro do not display permanent cellular drift and they permit expression of the phenotypic (organoid) characteristics of the original tumor when passaged in nude mice. Thus, human tumor cells maintained in vitro may reexpress biochemical (CEA synthesis) and morphologic (microscopic) properties of their histogenetic origin by periodic, short-term (7-10 days) passage through xenogeneic hosts. (33 refs.)

77-6504 The Radiological Investigation of Colonic Epithelial Dysplasia and Latent Carcinoma in Chronic Ulcerative Colitis -- Preliminary Observations (Meeting Abstract). (Eng.) Frank, P. H. (Dept. Radiology, Univ. Chicago, Chicago, IL 60637); Riddell, R. H.; Levin, B.; Feczko, P. J. *Clin Res* 25(4): 607A; 1977. (no refs.)

77-6505 **Carcinoma of the Large Bowel in Uganda.** (Eng.) Ssali, J. C. (Dept. Surgery, Makerere Univ., Kampala, Uganda). *Ann R Coll Surg Engl* 59(5): 420-422; 1977.

Forty-one cases of carcinoma of the large bowel seen in Uganda between 1969 and 1976 are reviewed. The young average age of the patients (47.7 yr) is remarkable, as is the conclusion that diet probably played no role in the etiology. Most of the lesions occurred in the lower rectum. (5 refs.)

77-6506 **Is Gardner Syndrome a Distinct Genetic Disorder? (Letter to Editor)** (Eng) Danes, B. S. (Lab. Cell Genetics, Dept. Medicine, Cornell Univ. Medical Coll., New York, NY 10021); Krush, A. J.; Gardner, E. J. *Lancet* 2(8044): 925; 1977.

A study of 17 families with adenomatosis of the colon and rectum revealed that some or all of the extracolonic growths associated with Gardner syndrome were present in 10 of the families. Skin cancer was found in 6 of these 10 families, and increased tetraploidy was noted in cultures from patients with extracolonic growths. These studies provide further evidence that Gardner syndrome forms a distinct group among patients with adenomatosis of the colon and rectum. (4 refs.)

77-6507 **The Natural History of Hypertrophic Gastropathy (Menetrier's Disease). Report of a Case with 6 Year Follow-up and Review of 120 Cases from the Literature.** (Eng) Scharschmidt, B. F. (Dept. Gastroenterology, 120 HSW, Univ. California Medical Center, San Francisco, CA 94143). *Am J Med* 63(4): 644-652; 1977.

A 33-yr-old black man was diagnosed as having hypertrophic gastropathy after laparotomy and gastrotomy revealed a large, thick-walled stomach with giant rugal-folds from fundus to antrum. Microscopically, no neoplastic changes were seen. At his death 16-yr later, persistent hypertrophic gastropathy and a hepatocellular carcinoma metastatic to the stomach and regional lymph nodes were diagnosed. Data from 120 literature cases suggest that gastric carcinoma frequently develops in these patients. (93 refs.)

77-6508 **Characterization of a Spontaneous Esophageal Squamous Cell Carcinoma from a Rhesus Monkey (*Macaca mulatta*) and the Establishment of an Epithelial Cell Line (Meeting Abstract).** (Eng) Neubauer, R. H. (Frederick Cancer Res. Center, Frederick, MD 21701); Rabin, H.; Hopkins, R. H.; Valerio, M. G.; Gonda, M. A. *In Vitro* 13(3): 74; 1977. (no refs.)

77-6509 **Factors in Isolation of Continuous Cell Lines from Small Cell Anaplastic Carcinoma of the Lung (Meeting Abstract).** (Eng) Pettengill, O. S. (Dartmouth Medical School, Hanover, NH 03755); Sorenson, G. D.; Maurer, L. H. *In Vitro* 13(3): 176; 1977. (no refs.)

77-6510 **Cellular Changes in Apparently Normal Human Lung Tissue Grafted into Nude Mice (Meeting Abstract).** (Eng) Arnoux, B. (Laboratoire de Pathologie Pleuro-pulmonaire, Hopital Laennec, 42 rue de Sevres, 75007 Paris, France); Stanislas, G.; Masse, R.; Chretien, J. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 46; 1977. (no refs.)

77-6511 **Surface Morphology of the Human Alveolar Macrophage.** (Eng) Quan, S. G. (Div. Hematology-Oncology, Dept. Medicine, UCLA Sch. Medicine, Los Angeles, CA 90024); Golde, D. W. *Exp Cell Res* 109(1): 71-77; 1977.

Scanning electron microscopy studies of alveolar macrophages obtained by bronchopulmonary lavage from normal smokers and nonsmokers are presented. The macrophages, which ranged in size from 8 μ m in diameter to > 100 μ m in length, were examined after various time intervals in vitro. Macrophages from smokers attached to and spread faster on the substrate than those from nonsmokers. They also had more lamellipodia, filopodia, blebs, and microvilli than nonsmoker macrophages. Smoker macrophages cultured for 72 hr had the typical morphology of cultured macrophages seen at the light microscope level, but nonsmoker macrophages were noticeably different. When iron or carbon was added to the culture, cells ingesting the particles were more spherical and elongated, they had 10 times more blebs and membrane convolutions, and they had filopodia at or near the periphery, especially those cultured with iron. These studies suggest an important relationship between function and morphology in macrophages from smokers and nonsmokers. (25 refs.)

77-6512 **Cancer of the Nasopharynx in Two Brothers.** (Rus) Chizh, G. I. (Dept. Head and Neck Tumors, Rostov Scientific Res. Inst. Oncology, Rostov, USSR); Rozhkova, N. I.; Dorfman, S. M. *Vestn Otorinolaringol* (4): 81-82; 1977.

Poorly differentiated squamous-cell carcinoma of the nasopharynx was diagnosed in a 63-yr-old man, and, 9 mo later, in his 66-yr-old brother. They had lived in the same town all their lives, had never smoked, and had never been exposed to carcinogens occupationally. A third brother, aged 70 yr, is healthy. (6 refs.)

77-6513 Multiple Hepatic Tumors and Peliosis Hepatis in Fanconi's Anemia Treated with Androgens.

(Eng) Shapiro, P. (Dept. Surgery, Sch. Medicine and Sacramento Medical Center of the Univ. California, Davis, CA); Ikeda, R. M.; Ruebner, B. H.; Connors, M. H.; Halsted, C. C.; Abildgaard, C. F. *Am J Dis Child* 131(10): 1104-1106; 1977.

A 13-yr-old boy with a 5-yr history of Fanconi's anemia had been treated with prednisone and testosterone propionate or oxymethalone. Two months before his death, he developed severe varicella with pneumonia, jaundice, and fever. Autopsy revealed peritonitis secondary to focal necrotizing colitis and multiple hepatocellular neoplasms. The association of androgenic steroids with hepatic neoplasms is discussed. It is suggested that these steroid-induced hepatic neoplasms, which resemble hepatocarcinomas histologically, but are characterized by lack of metastases and reversibility, be renamed. (20 refs.)

77-6514 A Case of Minimal Deviation Hepatoma in Man with Elevated Liver-Type Pyruvate Kinase Isozyme. (Eng) Taketa, K. (First Dept. Internal Medicine, Okayama Univ. Medical Sch., Shikatacho 2-5-1, Okayama 700, Japan); Ueda, M.; Watanabe, A. *Gann* 68(1): 29-35; 1977.

The results of an enzyme analysis of a liver tumor (6 x 6 x 5 cm) removed from a 57-yr-old man are reported. The tumor was classified as a well-differentiated hepatocellular carcinoma, but the lack of necrotic mass in the tissue could also have resulted in its classification as a slow-growing hepatoma. The activities of the adult-type liver enzymes were high and those of the fetal-type liver enzymes of carbohydrate metabolism were low. Glucokinase activity was absent, fructose-1,6-bisphosphatase was reduced, and hexokinase types I and III and glucose-6-phosphate dehydrogenase were slightly increased. Aniline hydroxylase was close to normal and there was a more or less differentiated pattern of alcohol dehydrogenase. Thus, the enzyme profile was comparable to that of minimal deviation hepatomas in the rat. The tumor was also found to have above-normal levels of pyruvate kinase type L and below-normal levels of type M₂ (1.21 and 0.12 unit/mg protein, respectively). The electrophoretic and kinetic properties of the L pyruvate kinase were indistinguishable from those of a normal liver. It is suggested that the disordered regulation of protein synthesis during hepatoma gene expression accounted for the above-normal type L activity; this could also explain the subnormal level of the type M₂ enzyme. (32 refs.)

77-6515 Ultracytochemical Localization of Glucose-6-phosphatase in Chang Rat Hepatoma In Vivo and In Vitro. (Eng) Moller, P. C. (Div. Cell Biology, Dept.

Human Biological Chemistry and Genetics, Graduate Sch. Biomedical Sciences, Univ. Texas Medical Branch, Galveston, TX 77550); Yokoyama, M.; Chang, J. P. *J Natl Cancer Inst* 58(5): 1401-1405; 1977.

The standard lead precipitation method was used for the ultracytochemical localization of glucose-6-phosphatase (G-6-Pase) in in vivo and in vitro Chang rat hepatomas and in normal adult rat liver. The enzyme was localized in the cisternae of the nuclear envelope and endoplasmic reticulum. Cytochemically, the amount of G-6-Pase reaction product was reduced in the hepatomas compared with normal liver hepatocytes. These results are in agreement with biochemical studies suggesting a reduction in G-6-Pase activity in other rat hepatomas. (25 refs.)

77-6516 Effect of the Inoculum Size of Cells on the Maintenance of Diploidy in Cultured Liver Cells of the Rat. (Eng) Nakabayashi, H. (Div. Pathology, Cancer Inst., Okayama Univ. Medical Sch., Shikatacho 2-5-1, Okayama 700, Japan); Sato, J. *Gann* 68(1): 21-27; 1977.

The relationship between chromosomal changes in vitro and inoculum size at subculturing and the conditions necessary for maintaining a normal diploid karyotype were investigated in rat J-5-2 cells. This line exhibited a high degree of diploidy for 200 days after the last cloning (diploid line), but, thereafter, pseudodiploid cells gradually increased in number (pseudodiploid line). The population-doubling times of these lines were almost the same; however, the pseudodiploid line had a higher saturation density and the diploid line had a higher plating efficiency. Neither line grew at inocula < 3 x 10⁵ cells/flask. With a large inoculum (3 x 10⁶ cells/flask), the diploid cells showed an increase of pseudodiploidy, but when the inoculum was 3 x 10⁵ cells, > 80% of the cells maintained the diploid karyotype. Pseudodiploid cells showed an increase in pseudodiploid cells with a large inoculum and an increase in diploid cells with a small inoculum size. Thus, subculturing with a small inoculum is useful for maintaining diploid cells in vitro. The pseudodiploid line had three marker chromosomes, all involving chromosome 1. Both diploid and pseudodiploid cells maintained their epithelial features throughout the experiment. (24 refs.)

77-6517 Observations on Squamous Cell Carcinomas of Sheep in Queensland, Australia. (Eng) Ladds, P. W. (Dept. Tropical Veterinary Science, James Cook Univ. North Queensland, Queensland 4823, Australia); Entwistle, K. W. *Br J Cancer* 35(1): 110-114; 1977.

The occurrence of squamous cell carcinoma in sheep pastured in Queensland, Australia, was recorded over a 4-yr period. There were 146 lesions in 132 sheep, 76% on the ears. Tumor incidence increased with advancing age, and ewes were more susceptible (95%) than wethers. Autopsy reports

of four ewes are presented. The tumors grew at a rate of 0.3 to 0.4 cm/mo. It is suggested that factors other than solar radiation per se are involved in the genesis of these tumors. Ovine aural squamous cell carcinoma could be useful in studying skin cancer in humans. (11 refs.)

- 77-6518 **Burn Scar Carcinoma: A Review and Analysis of 46 Cases.** (Eng) Novick, M. (Northside Medical Center, 13550 N. 31st St., Suite 320, Tampa, FL 33612); Gard, D. A.; Hardy, S. B.; Spira, M. *J Trauma* 17(10): 809-817; 1977.

In a series of 46 patients who developed burn scar carcinoma, the av time between the burn (44 thermal, 1 radiation and 1 electrical) and the diagnosis of cancer, usually squamous cell carcinoma, was 42.3 yr, with a range of 1.5 to 75 yr. Sixteen patients had metastases and five developed recurrences. The development of the cancers is discussed in light of anatomic location and histology and the promoting or co-carcinogenic role of trauma. (23 refs.)

- 77-6519 **Ultrastructure of Oral Squamous-cell Carcinoma.** (Eng) Chen, S. Y. (Temple Univ. Sch. Dentistry, Dept. Pathology, 3223 North Broad St., Philadelphia, PA 19140); Harwick, R. D. *Oral Surg* 44(5): 744-753; 1977.

The ultrastructure of oral epidermoid carcinoma was investigated in 16 specimens classified as moderately differentiated. Specific histological characteristics correlated with hyperactivity, phagocytosis, locomotion, and differentiation; these correlations are analyzed. (11 refs.)

- 77-6520 **Squamous Cell Carcinoma Arising in Hidradenitis Suppurativa.** (Eng) Gordon, S. W. (Dept. Surgery, Methodist Hosp., Indianapolis, IN). *Plast Reconstr Surg* 60(5): 800-802; 1977.

A 28-yr-old woman developed squamous cell carcinoma in a postsacral lesion of hidradenitis suppurativa 17 yr after diagnosis of the disease. Metastatic carcinoma was diagnosed 12 mo later. The literature is briefly reviewed. (11 refs.)

- 77-6521 **Xeroderma Pigmentosum.** (Fre.) Brehant, J. (3, rue Jean-Goujon, 75008 Paris, France) *Bull Acad Natl Med (Paris)* 161(3): 229-231; 1977.

From 1958 to 1966, 32 cases of xeroderma pigmentosum were observed at the Pierre and Marie Curie Institut in Algiers. The increased incidence is explained by the fact that the patients were from the Sahara region. Epitheliomatosis almost always appears before 7 yr of age; in 75% of the cases seen here, it occurred before the age of 30. Three rare cases involved adults (1 woman, 20 yr old; 2 men, 23 and 48 yr old). All patients except the three adults with the disease died before the age of 15. As in other recessive syndromes, these children are often underdeveloped, weak, and sometimes retarded. Various therapeutic approaches (β radiation, radiophosphorus therapy) are reviewed, and their respective efficacies are compared. It is suggested that exposure to the sun be avoided and that the skin be protected with various vitamin creams and corticoids. (2 refs.)

- 77-6522 **A Case of Multiple Epidermoid Carcinoma in a Patient with Psoriasis.** (Rus) Bogdanov, G. I. (Dept. Skin and Venereal Diseases, Gorki Medical Inst., Gorki, USSR). *Vestn Dermatol Venerol* (8): 68-69; 1977.

Multiple squamous cell carcinomas of the extremities and abdominal region were found in a 43-yr-old man who had suffered from psoriasis for 19 yr. It is suggested that the regenerative process in psoriasis may lead to neoplasia. (no refs.)

- 77-6523 **Morphology of Multiple Cylindroma of the Skin (Histochemical and Electron Microscopic Study).** (Rus) Dikshtein, E. A. (Dept. Pathological Anatomy, A. M. Gorkii Donetsk Medical Inst., Donetsk, USSR); Torsuev, N. A.; Romanenko, V. N.; Shevchenko, N. I.; Merezko, V. A. *Arkh Patol* 39(7): 58-62; 1977.

Electron microscopic studies of multiple cylindromas found in a 52-yr-old woman showed that these tumors originated from the sweat glands, apparently the apocrine glands. Tumor cells and stromal fibroblasts were involved in the formation of the hyaline substance. (20 refs.)

- 77-6524 **Metastasis to the Pericardium from Squamous Cell Carcinoma of the Cervix.** (Eng.) Charles, E. H. (Gynecologic Oncology Section, Dept. Obstetrics and Gynecology, New York Medical Coll., 1249 Fifth Ave., New York, NY 10029); Condori, J.; Sall, S. *Am J Obstet Gynecol* 129(3): 349-351; 1977.

The case of a 46-yr-old woman with pericardial metastasis of cervical carcinoma is presented. Metastases were noted 21

mo after diagnosis and initial treatment. This case is unusual because the spread was confined to a single organ. (2 refs.)

- 77-6525 Malignant Transformation (Epidermoid Epithelioma) of an Ovarian Dermoid Cyst. (Ita.)**
Papadia, L. (Ospedali Riuniti di Napoli, Ospedale "A. Cardarelli", Naples, Italy); Di Maro, L.; Guida, A. *Rass Int Clin Ter* 57(6): 385-392; 1977.

A rare case of dermoid ovarian cyst with malignant epithelomatous transformation occurred in a 39-yr-old woman. For the previous 2 yr, the patient had exhibited irregular menstrual cycles with amenorrhea and oligomenorrhea, followed by an increase in abdominal volume, asthenia, and loss of wt. Antiinflammatory drugs produced negative results. Surgery was performed with satisfactory results; however, 13 mo later a relapse occurred with ascites, pain in the lumbar-sacral region, and multiple bone metastases. (14 refs.)

- 77-6526 Ovarian Neoplasia in Ornamental Hybrid Carp (Nishikigoi) in Japan. (Eng)** Ishikawa, T. (Dept. Experimental Pathology, Cancer Inst., Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan); Takayama, S. *Ann NY Acad Sci* 298: 330-341; 1977.

A total of 21 massive abdominal tumors were found in 4- to 6-yr-old carp collected from different hatcheries in northern Japan over a 2-yr-period. Histologically, the tumors varied greatly, with areas resembling human dysgerminomas, granulosa theca cell tumors, embryonal carcinomas, and fibromas. All tumors were classified as ovarian in origin, with 19/21 fish identified as females and ovarian tissue identified adjacent to 15 tumors. (28 refs.)

- 77-6527 Chromosomes 1 in 14 Ovarian Cancers. Heterochromatin Variants and Structural Changes. (Eng.)** Atkin, N. B. (Dept. Cancer Res., Mount Vernon Hosp., Northwood, Middlesex, HA6 2RN, England); Pickthall, V. J. *Hum Genet* 38(1): 25-33; 1977.

Structural changes in chromosome 1 were studied in 14 malignant ovarian cancers surgically removed from patients aged 21 to 83 yr. In tumor cells from four patients, a pericentric inversion of the heterochromatic region of the chromosome was noted. One of these patients had two or three ring chromosomes with large C bands; these were possibly derived from chromosome 1. Two tumors had two number 1 chromosomes of similar length as well as another subtelocentric

chromosome of similar length with two C bands, possibly of chromosome 1 origin. In the remaining eight patients there were two abnormal chromosomes derived from chromosome 1 with additional or deleted material on one or both arms. Multiple double-minute chromatin bodies were found in all tumor metaphases of one patient and 30% of those of another. These findings suggest that chromosome 1 involvement is specific for ovarian cancer or that it is somehow associated with the later stages of the disease. (14 refs.)

- 77-6528 Morphological Aspects of the Tumor-Free Mammary Gland in BALB/c/Cb/Se Mice with an Induced Carcinoma of the Contralateral Breast. (Ita.)** Biancifiore, C. (Universita degli Studi Perugia, Istituto di Anatomia e Istologia Patologica, Perugia, Italy). *Lav Ist Anat Istol Patol Perugia* 37(1): 19-28; 1977.

Tumor-free mammary glands obtained from intact virgin and ovariectomized BALB/c/Cb/Se (BALB/c) mice either untreated (226 mice) or treated (354 mice) with estrone, 20-methylcholanthrene, and 3,4-benzopyrene for 7-8 wk exhibited various pathological changes: secretion, dilated ducts and hyperplastic alveolar and precancerous nodules. (The treated mice had a carcinoma in the contralateral breast). The highest incidence of lesions occurred in intact virgin mice (327 lesions in 186 animals) and the lowest, in ovariectomized mice (125 lesions in 122 animals). Hyperplastic alveolar (68) and precancerous (23) nodules prevailed in the treated intact mice, and they are considered to be morphological precursors of cancer. They are found most commonly in mice that have a higher frequency of mammary carcinomas, and they are absent in untreated mice. (11 refs.)

- 77-6529 Histopathogenesis of 7,12-Dimethylbenz[a]anthracene-induced Rat Mammary Tumors. (Eng)** Haslam, S. Z. (Dept. Zoology, Univ. California, Berkeley, Berkeley, CA 94720); Bern, H. A. *Proc Natl Acad Sci USA* 74(9): 4020-4024; 1977.

Studies were performed to investigate the histopathogenesis of mammary carcinomas in virgin Lewis strain rats fed 7,12-dimethylbenz[a]anthracene (DMBA) intragastrically at 0.015 g/100 g body wt. Mammary gland dysplasias were also transplanted to the inguinal gland-free mammary fat pad and investigated. Three types of dysplasia were noted: hyperplastic alveolar nodules (HAN), terminal ductal hyperplasia (TDH) and regressed tumor site. HANs filled the fat pad upon transplantation and were lobuloalveolar, ductoalveolar or cystic alveolar. Six of 113 outgrowths produced mammary carcinomas: of 4 of these tumors classified, 3 were ovarian dependent and 1 was ovarian independent. Transplantation of six TDHs gave rise to three palpable carcinomas which

subsequently regressed. The number of treated animals with HANs reached 100% by 45 days and remained constant. At 45 and 60 days, more rats had TDHs than mammary carcinomas; by 75 and 90 days, the numbers were about equal; and the situation was reversed at 120 and 365 days. Progressively growing tumors (PGT) appeared to originate within the terminal ductules. The first palpable tumors were noted and all regressed. Of nine spontaneously regressing tumors (SRT) that occurred, four regrew, two progressively. Transplanted SRTs grew sporadically and regressed. PGTs occurred by 3 mo, and 70% were ovarian dependent. Of 24 tumors occurring by 12 mo, 37% were SRTs, 42% were ovarian dependent and 21% were ovarian independent. Thirty percent of the rats developed only PGTs, 5% developed only SRTs and the remainder developed both. PGTs frequently regressed initially after transplantation. Thirty-six ovarian dependent transplants grew into tumors surrounded by abnormal ductal outgrowths; all regressed after ovariectomy. The histology of the tumors is presented. (31 refs.)

77-6530 Sex Chromatin in Women with Breast Cancer, Leukemia, Lymphoma, and Hypertension (Letter to Editor). (Eng) Spiers, A. S. (Boston Univ. Medical Center, Boston, MA); Turner, J. E. *JAMA* 238(17): 1812-1813; 1977.

Fresh buccal smears from 250 female patients with breast cancer, leukemia, and lymphoma were stained to determine the incidence of X-chromosome numerical abnormalities in these women and to determine whether breast cancer or cytotoxic treatment alters the incidence or expression of the sex chromatin. No double-chromatin-positive or chromatin-negative women were found. The incidence of X bodies and the sex chromatin distribution were identical in all patients, including additional patients tested with nonmalignant blood disease, minor surgery, or hypertension. Cytotoxic drugs and/or radiotherapy did not change these findings. (8 refs.)

77-6531 Thymus and Breast Cancer--Plasma Androgens, Thymic Pathology, and Peripheral Lymphocytes in Myasthenia Gravis. (Eng) Papatestas, A. E. (Dept. Surgery, Mount Sinai Sch. Medicine, City Univ. New York, Fifth Ave. and 100th St., New York, NY 10029); Mulvihill, M.; Jenkins, G.; Kornfeld, P.; Aufses, A. H.; Wang, D. Y.; Bulbrook, R. D. *J Natl Cancer Inst* 59(6): 1583-1588; 1977.

Plasma androgen sulfates were measured in 92 women with myasthenia gravis (MG) to determine whether there was any association between these levels and thymic pathology, peripheral lymphocyte counts, or risk of neoplasia. Plasma androgen sulfate concentrations and thymic pathology were significantly associated in patients with nonthymomatous MG.

Patients who had many germinal centers at thymectomy had lower levels of dehydroepiandrosterone sulfate (DS) and androsterone sulfate (AS) compared with those with no or few germinal centers, and this held for all age groups. This relationship was not due to duration or severity of disease. DS values were significantly associated with age, but germinal centers were associated with DS independently of age. No association between subnormal androgens and other high risk factors for breast cancer were detected in these women. A weak but positive correlation was found between peripheral lymphocyte counts and plasma DS levels, but there was no correlation between lymphocytes and AS levels. Thymectomy led to a significant and immediate fall in plasma DS levels but not in AS levels; however, no difference was found between overall pre- and postthymectomy values of DS or AS. AS and DS levels in MG patients with breast cancer were markedly depressed. The lowest levels were observed in women with previous bilateral breast cancer who developed a second primary breast lesion prior to the DS and AS determinations. (26 refs.)

77-6532 Small Cell Carcinoma of the Male Breast. Report of a Case. (Eng.) Yogore, M. G. (Dept. Pathology, Univ. Illinois at the Medical Center, 840 South Wood St., Chicago, IL 60612); Sahgal, S. *Cancer* 39(4): 1748-1751; 1977.

Light and electron microscopy were used to study an uncommon type of breast cancer in a 56-yr-old black man. Histologic and ultrastructural characteristics were identical to infiltrating lobular carcinoma in the female breast. There was no history of estrogen administration. (17 refs.)

77-6533 So-called Transitional-cell Carcinoma of the Prostate and Its Oncogenesis. (Ger.) Kofler, K. (Pathologisch-bakteriologisches Institut, Allgemeine Poliklinik der Stadt Wien, Simmeringer Hauptstrasse 81-85/III/5, A-1110 Vienna, Austria); Schmidbauer, C. *Z Nephrol Urol* 70(8): 569-575; 1977.

Histogenetic aspects of transitional cell carcinoma (TCC) of the prostate are discussed in connection with two new cases in patients aged 58 and 80 yr. Intracanalicular carcinoma in situ with sporadic infiltration of the prostatic stroma was diagnosed in one patient who developed metastases to the corpora cavernosa of the penis a few months later. Grade III carcinoma with intracanalicular invasion and extensive infiltration of the stroma was found in the other patient 3 yr after removal of a prostatic adenoma. Literature data indicate frequent associations of TCC with adenomyomatosis, acinar adenocarcinoma, and mixed cell transitional cell adenocarcinoma of the prostate. The name TCC is incorrect, as this carcinoma does not always originate from the transitional epithelium; it develops mainly in the area of the transitional

epithelial islands, or from reserve cell hyperplasia, with carcinoma in situ as an intermediate stage. Neither infiltrating carcinoma nor carcinoma in situ can be distinguished morphologically and histochemically from carcinomatusly dedifferentiated transitional epithelium. Epithelial dysplasia is believed to be the precancerous stage of TCC in situ. Invasion of the stroma may not be obligatory; the latency is unknown. Early cases of TCC are usually symptom-free, but prostatism develops in more advanced cases. The prognosis is generally less favorable than that for adenocarcinoma. (21 refs.)

- 77-6534 **Characterization of a New Transitional Cell Carcinoma Line (Meeting Abstract).** (Eng) Moore, G. E. (Denver General Hosp., Denver, CO 80204); Swanson, T. L.; Morgan, R. T.; Quinn, L. A. *In Vitro* 13(3): 173; 1977. (no refs.)

- 77-6535 **Acinous Cell Carcinoma: A Histogenic Hypothesis.** (Eng) Batsakis, J. G. (Dept. Pathology, Univ. Michigan Medical Sch., Ann Arbor, MI 48109); Wozniak, K. J.; Regezi, J. A. *J Oral Surg* 35(11): 904-906; 1977.

Pathologic examination of a mucoepidermoid carcinoma of the parotid gland from a 39-yr-old man indicated that the tumor cells were of terminal duct origin. Thus some acinous cell carcinomas can be of intercalated duct origin rather than deriving from serous cells of the acinar part of the salivary unit. (8 refs.)

- 77-6536 **Ultrastructure of Chromophobe Adenoma of the Human Pituitary Gland.** (Eng.) Roy, S. (Dept. Pathology, All India Inst. Medical Sciences, New Delhi 11016, India). *J Pathol* 122(4): 219-223; 1977.

An ultrastructural study of pituitary chromophobe adenoma, including 12 specimens of "nonfunctioning" tumors and 4 associated with acromegaly, revealed varying degrees of granularity in most cells of all tumors. However, two distinct morphological types of chromophobe tumors were noted. In one type, secretory granules were frequently seen in moderate or large numbers and the cells were poor in rough endoplasmic reticulum (RER) and Golgi apparatus. These cells were considered secretorily inactive storage cells, and they were the predominant cells in eight nonfunctioning adenomas. The other type, noted in four nonfunctioning adenomas and in all four adenomas with acromegaly, was generally poor in secretory granules but was rich in RER and Golgi apparatus, suggesting secretory activity. In acromegaly these features may indicate active hormone synthesis and secretion, but the morphological evidence of active secretion in the four nonfunctioning adenomas is not understood. (14 refs.)

- 77-6537 **Structure and Function of the Pituitary Gland in Gonadal Tumor-bearing and Normal Cyprinid Fish.** (Eng.) Leatherland, J. F. (Dept. Zoology, Coll. Biological Science, Univ. Guelph, Guelph, Ontario, Canada); Sonstegard, R. A. *Cancer Res* 37(9): 3151-3168; 1977.

Since one of the characteristics of the gonadal tumor-bearing cyprinid fish and also of non-tumor bearing (sterile) hybrids is a massive proliferation of pituitary basophils, an investigation was made to elucidate the pituitary-gonadal feedback axis in these fish. The F₁ generation hybrids of carp and goldfish exhibited a marked hyperplasia of the pars distalis basophil (gonadotrophic) cells. This first became evident in 3- to 4-yr-old fish, the age at which normal carp and goldfish become sexually mature. Many of these hybrids also developed gonadal tumors, the genesis of which coincided with the onset of gonadotroph proliferation. The basophil hyperplasia was more marked in the tumorous hybrids than in the nontumorous ones. Gonadotroph hyperplasia was also evident in tumor-bearing carp. Methallibure, a drug that inhibits gonadal development in cyprinids, caused a marked reduction of pituitary basophils in hybrid fish without affecting the histopathology of the tumor. This suggests that the onset of tumor proliferation, although coincident with the onset of gonadotroph proliferation, is not caused by increased gonadotroph activity. Gonadotroph proliferation in both tumor-bearing and nontumorous hybrids is probably related to the sterile condition of the fish rather than to the tumor itself. (41 refs.)

- 77-6538 **A Comparative Study of the Pretumorous Thyroid Gland of the Gynogenetic Teleost *Poecilia formosa*, and That of Other Poeciliid Fishes** (Eng) Woodhead, A. D. (Biology Dept., Brookhaven Natl. Lab., Upton, NY 11973); Scully, P. N. *Cancer Res* 37(10): 3751-3755; 1977.

A laboratory clone of the gynogenetic fish *Poecilia formosa* (the Amazon molly) showed a high incidence of invasive thyroid hyperplasia when inoculated with isogenic fish cells with damaged DNA. The sensitivity of the response indicated that the thyroid gland of this species might differ from that typically found in fish. Comparisons were made between the thyroid of *P. formosa* of several ages and that of five closely related species. In the five related species, the thyroid gland was composed of a few uniform, colloid-filled follicles lined with cuboidal epithelial cells that were scattered around the ventral aorta. The thyroid of *P. formosa* was much larger and contained numerous microfollicles and a follicular group of epithelial cells. The follicular cells were hypertrophied and there was hyperplasia of the connective tissue. The extent of these atypical elements increased with advancing age. The changes in the thyroid of *P. formosa* resembled those seen in the development of thyroid tumors in some highly inbred fish strains. It is concluded that *P. formosa* is a useful test animal for oncogenic studies. (15 refs.)

7-6539 **Parathyroid Carcinoma in Familial Hyperparathyroidism.** (Eng) Dinnen, J. S. (Dept. Pathology, Welsh Natl. Sch. Medicine, Univ. Hosp., Wales); Greenwood, R. H.; Jones, J. H.; Walker, D. A.; Williams, E. D. *Clin Pathol* 30(10): 966-975; 1977.

Two families with hereditary hyperparathyroidism are described. One member of each family developed a parathyroid carcinoma that, in one case, recurred locally and metastasized. This patient showed hyperplasia of one of the three parathyroid glands. The different parathyroid lesions found in familial hyperparathyroidism could be the result of progression from hyperplasia to the formation of benign or malignant tumors. The remaining hyperplastic glands may be suppressed by hypercalcemia. There was no evidence of multiple endocrine neoplasia in either family. Three members of the first family had ichthyosis and both affected members of the second family had jaw tumors, one of which was an ossifying fibroma, suggesting a possible association of these conditions with familial hyperparathyroidism. (30 refs.)

7-6540 **Thyroid Cancer in an Iodide Rich Area: A Histopathological Study.** (Eng.) Williams, E. D. (Dept. Pathology, Welsh Natl. Sch. Medicine, Heath Park, Cardiff, CF4, 4XN, Wales) Doniach, I.; Bjarnason, O.; Mies, W. *Cancer* 39(1): 215-222; 1977.

A comparison was made of the incidence of different histological types of thyroid carcinoma in an area of high (Iceland) and normal (Northeast Scotland) iodide intake. Both areas have clearly defined populations served by a single pathology laboratory. All definite and dubious thyroid carcinomas from both regions were examined and classified by the same two pathologists. The age-specific incidence rates for papillary carcinoma in each area rose with age; they were five times higher in Iceland than in Northeast Scotland. The numbers of follicular carcinomas were small, and this tumor was relatively less frequent in Iceland than in Aberdeen. These findings, together with the known high relative frequency of follicular carcinoma and low frequency of papillary carcinoma in areas of endemic goiter, suggest that the incidences of papillary carcinoma and follicular carcinoma are influenced separately by dietary iodide. No evidence implicating lymphocytic thyroiditis, radiation, or genetic factors in the genesis of thyroid carcinoma in Iceland or Northeast Scotland was found. Undifferentiated carcinoma was about three times common in Iceland as in Northeast Scotland. Malignant lymphoma of the thyroid was surprisingly common in Northeast Scotland, possibly because of the high frequency of thyroiditis in this region. These studies suggest that the incidence of different histological types of thyroid malignancy is influenced by different etiological factors. They also provide support for the subdivision of thyroid malignancy into different types and for the general importance of accurate histological typing in cancer epidemiology. (31 refs.)

77-6541 **Solitary Thyroid Nodules.** (Eng) Liechty, R. D. (Dept. Surgery, Univ. Colorado Medical Center, 4200 E. Ninth Ave., Denver, CO 80220); Stoffel, P. T.; Zimmerman, D. E.; Silverberg, S. G. *Arch Surg* 112(1): 59-61; 1977.

Sixty-seven patients with solitary thyroid nodules who underwent thyroid surgery at Colorado General Hospital during the years 1965 through 1975 were investigated. The criteria used to select these patients, none of whom had a history of radiation to the head or neck area, were designed to minimize the probability of cancer. The incidence of malignancy was 17.9% (12 patients). This result compares with those of recent studies made in Chicago, Boston, and Michigan, but it is three times greater than the incidence of 5.7% found 11 yr ago in a study of 299 patients from a Midwestern university hospital. Perhaps the increased frequency of cancer is due to the more careful selection of patients for whom surgical diagnosis is recommended. (12 refs.)

77-6542 **Cancer of the Thyroid Body: Ultrastructural and Histochemical Studies.** (Fre) Chomette, G. (Service Central d'Anatomie pathologique, UER Pitie-Salpetriere, 83, bd de l'Hopital, 75013 Paris, France); Auriol, M.; Garnier, H. *Arch Anat Cytol Pathol* 25(3): 161-173; 1977.

A histochemical and ultrastructural study of 21 thyroid carcinomas, including 4 anaplastic and 6 medullary carcinomas, is presented. In the common forms of thyroid carcinoma, all intermediate cell types can be observed. They range from highly differentiated cells, which are comparable to normal cells but contain an excessively large number of mitochondria, to simplified cells having almost no specialized functions. Certain peculiarities of the nucleus (pseudoinclusions, nuclear bodies, a large nucleolus) suggest a disturbance of the nuclear-cytoplasmic exchange in these cells. Abnormalities of the basal membrane reflect, at each stage of differentiation, more- or less-severe metabolic alterations in the cancer cell. In medullary carcinoma, florid forms can be distinguished from cytolytic forms and the abundance of amylose is proportional to the cellular changes. The membranous deposits found in the connective tissue stroma are derived from the stromal myofibroblasts and not from the epithelial cells. The histochemical studies revealed generally increased enzyme activities. NAD activity was highest in papillary and medullary carcinomas and vesicular epithelioma, malate dehydrogenase activity was highest in papillary carcinoma, and adenosine triphosphatase activity highest in medullary carcinoma and vesicular epithelioma. Lactate dehydrogenase was increased in all tumor types, including anaplastic carcinoma. (57 refs.)

77-6543 **Tumors of the Brachial Plexus Associated with a Tumor of the Thyroid Gland.** (Eng) Noterman,

J. (Dept. Neurosurgery, Hopital St. Pierre, 1 rue Heger-Bordet, 1000 Bruxelles, Belgium); Dor, P.; Jortay, A. M. *World J Surg* 1(5): 683-684; 1977.

The case reports of a 37-yr-old man with a follicular carcinoma of the thyroid and a benign schwannoma of the brachial plexus, a 59-yr-old woman with a papillary carcinoma of the thyroid and a schwannoma of the brachial plexus, and a 57-yr-old woman with a large colloid goiter and a neurofibrosarcoma of the brachial plexus are presented. Although these tumors differed in pathologic features and origin, approx 10% of the reported brachial plexus schwannomas have had associated thyroid tumors. (9 refs.)

77-6544 **A Human Malignant Schwannoma Cell Line** (Meeting Abstract). (Eng) Helson, C. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Helson, L.; Das, S. K.; Rubenstein, R. *In Vitro* 13(3): 154; 1977. (no refs.)

77-6545 **Oral Granular-Cell Tumors. Report of Twenty-Five Cases with Electron Microscopy.** (Eng.) Miller, A. S. (Temple Univ. Sch. Dentistry, 3223 N. Broad St., Philadelphia, PA 19140); Leifer, C.; Chen, S. Y.; Harwick, R. D. *Oral Surg* 44(2): 227-237; 1977.

Electron microscopy of oral granular cell tumors (granular cell myoblastoma) revealed the presence of four distinct types of cytoplasmic granules. Three types were interpreted as being lysosomal structures in different phases. The fourth type was an aggregate of viruslike particles. Other ultrastructural features of the granular cells included cytoplasmic processes containing five filaments (similar to neurites), deep invaginations of the plasma membrane (resembling Schwann cells), and the presence of desmosomal junctions, all strongly suggestive of a neural origin for the tumor cells. (26 refs.)

77-6546 **Granular Cell Myoblastoma.** (Eng.) Chrestian, M. A. (Laboratoire de Neuropathologie, Faculte de Medecine, Bd. Jean Moulin, 13385 Marseille, Cedex IV, France); Gambarelli, D.; Hassoun, J.; Gola, R.; Toga, M.; Bonerandi, J. J. *J Cutan Pathol* 4(2): 80-89; 1977.

Light and electron microscopy were used to examine three specimens of granular cell myoblastoma of the tongue. The results show that two different types of cells are present: granular cells with clear tubular processes and satellite fibroblasts most likely corresponding to stroma cells. However, it is emphasized that these ultrastructural findings cannot be proof of any definitive histogenetic hypothesis. (16 refs.)

77-6547 **Meningioma and Intracranial Hemangiopericytoma. A Comparative Electron Microscopic Study.** (Eng.) Pena, C. E. (Dept. Pathology, Mercy Hosp. and Univ. Pittsburgh Sch. Medicine, Pride and Locust Sts., Pittsburgh, PA 15219). *Acta Neuropathol* 39(1): 69-74; 1977.

Seven meningiomas and two intracranial hemangiopericytomas were studied using electron microscopy. Fundamental morphologic differences between the two tumor types were observed; one of the most significant was the presence of ultrastructural features suggesting leiomyoblastic differentiation in hemangiopericytoma. (28 refs.)

77-6548 **Melanotic Neuroectodermal Tumor of Infancy: Its Histological Similarities to Fetal Pineal Gland.** (Eng) Dooling, E. C. (Dept. Pathology, Children's Hosp. Medical Center, 300 Longwood Ave., Boston, MA 02115); Chi, J. G.; Gilles, F. H. *Cancer* 39(4): 1535-1541; 1977.

Striking similarities were found between the pineals of 107 fetuses and infants and a pigmented neuroectodermal tumor occurring in the right orbital and right frontal regions of a 6-mo-old boy. Both the human fetal pineal and melanotic neuroectodermal tumors of infancy are characterized by pigmented (melanin) epithelial cells, small undifferentiated cells and a fibrovascular stroma. The fetal pineal may be a normal precursor of the melanotic neuroectodermal tumor of infancy, or melanin production may be a normal function of differentiating neuroepithelial cells. (13 refs.)

77-6549 **Platelet-Cancer Cell Interaction in Metastasis Formation: A Possible Therapeutic Approach to Metastasis Prophylaxis.** (Eng.) Gastpar, H. (Dept. Otorhinolaryngology, Head and Neck Surgery, Univ. Munich Medical Sch., Munich, W. Germany). *J Med* 8(2): 103-114; 1977.

With the accumulation of evidence showing that anticoagulants and fibrinolytic drugs interfere with the initial adherence of cancer cells to the vascular endothelium and their enmeshment in a fibrin clot (a process believed to be related to the early stage of metastasis), clinical trials were undertaken using some previously investigated inhibitors of platelet aggregation. Initial studies with rats inoculated iv with Walker-256 carcinosarcoma cells demonstrated that several compounds, dipyridamole, 2,6-bis(diethylamino)-4-piperidinopyrimido-5,4-d-pyrimidine (RA 223), 2-(2-aminoethyl)amino-4-morpholinethieno-3,2-d-pyrimidine dihydrochloride (VK 744), the methylxanthine derivative pentoxifylline, and bencyclane were effective in decreasing the

incidence of fatal tumor cell embolism of the lungs, reducing platelet count, and decreasing cancer cell adherence, as observed in the rat mesentery. RA 233 and VK 744 were the most effective of the substances tested. RA 233 was chosen for human clinical trials on metastasis prophylaxis, as it was tolerated well with no severe side effects and it could be used for daily, long-term treatment. In 38 patients with sarcoma or malignant lymphoma of the head and neck region who had undergone surgery and radiation therapy, RA 233 treatment decreased the appearance of metastases significantly as compared with the same number of untreated matched controls. (25 refs.)

- 6550 **Behaviour of Multiple Primary Neoplasms.** (Eng) Taylor, T. V. (Dept. Clinical Surgery, Edinburgh Royal Infirmary, Edinburgh, Scotland); Torrance, B. *Br Med J* 2(6095): 1125; 1977.

The case reports of a 55-yr-old woman with six primary malignant neoplasms and a 48-yr-old man with five primary malignant neoplasms are summarized. None of the tumors metastasized, and both patients are alive and tumor-free. There was no family history of cancer in either case. It is suggested that in addition to a predisposition for multiple tumors, these patients had an altered immunological response that prevented tumor spread. (5 refs.)

- 6551 **A New Familial Cancer Syndrome? A Spectrum of Malignant and Benign Tumors Including Retinoblastoma, Carcinoma of the Bladder and Other Genitourinary Tumors, Thyroid Adenoma, and a Probable Case of Multifocal Osteosarcoma.** (Eng) Chan, H. (St. Jude Children's Res. Hosp., 332 N. Lauderdale, Memphis, TN 38101); Pratt, C. B. *J Natl Cancer Inst* 58(2): 205-207; 1977.

A 11-yr-old girl who had been cured of bilateral retinoblastoma subsequently developed non-radiation-induced osteosarcoma in multiple sites of the extremities. Investigation of the medical histories of 36 of her relatives through 6 generations revealed that 8 on the maternal side had malignant tumors, predominantly genitourinary carcinomas, 2 had benign tumors only, and 2 had both benign and malignant tumors. The paternal side of the family was cancer-free. The histologic variety of these tumors, the predominance of genitourinary carcinoma, the higher than expected frequency of tumor appearance over six generations, and the occurrence of malignant tumors in direct lineage suggest that the case of retinoblastoma followed by osteosarcoma is part of a familial cancer syndrome. (16 refs.)

- 6552 **Chromosomal Anomalies in Patients with Retinoblastoma.** (Eng) Wilson, M. G. (Div.

Genetics, Dept. Pediatrics, Univ. Southern California Sch. of Medicine, Los Angeles, CA); Ebbin, A. J.; Townner, J. W.; Spencer, W. H. *Clin Genet* 12(1): 1-8; 1977.

Among the karyotypes from 50 persons with histopathologically confirmed retinoblastomas, conventional staining and Giemsa banding revealed two chromosomal anomalies. A boy had a karyotype of 47,XXY, and another boy had an anomalous No. 13 chromosome with deletion of band 13q13 (the break points were assumed to be 13q12 and 13q14). These findings provided additional evidence that a deletion of chromosome No.13, most likely involving band 13q14, is associated with the development of retinoblastoma. An additional patient showed a chromosome constitution of 48,XXX,+21 upon reexamination. In conjunction with other reports, these findings also indicate that chromosomal aneuploidy may predispose children to the development of retinoblastoma. (32 refs.)

- 77-6553 **Identification of a Chromosome that Controls Malignancy in Chinese Hamster Cells.** (Eng) Bloch-Shtacher, N. (Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel); Sachs, L. *J Cell Physiol* 93(2): 205-212; 1977.

Chromosome studies were made of malignant Chinese hamster cells transformed by simian virus 40 (SV40), nonmalignant revertants from this line, their malignant segregants, and a malignant line transformed by methylcholanthrene. The transformed cells had a high degree of tumorigenicity in ICR nude mice and Chinese hamsters, but the four revertants derived from these cells did not form tumors. Isolation of the occasional colonies formed after the revertants were seeded in agar indicated that they were segregants. These agar segregants gave a 100% tumor incidence in nude mice and a 70% to 100% tumor incidence in newborn Chinese hamsters following injection of 10^6 cells. The transformed cells and their tumors had modal chromosome numbers of 26 and 27; the revertants and the agar segregants and their tumors had near triploid modal chromosome numbers. Compared to normal cells, transformed cells, segregants, and their tumors all had increased chromatin material of chromosome 3. There were no abnormalities in any of the other chromosomes. The cell line transformed by methylcholanthrene was more tumorigenic than the one transformed by the virus; it had a modal chromosome number of 23 and an additional long arm of chromosome 3. These findings indicate that an increase in chromosome 3 material is associated with malignancy in Chinese hamster cells. (32 refs.)

- 77-6554 **Marker Chromosome 14q+ Follicular Lymphoma in Transformation (Letter to Editor).** (Eng) Catovsky, D. (M.R.C. Leukaemia Unit, Royal Postgraduate Medical Sch., Hammersmith Hosp., London, W12

OHS, England); Pittman, S.; Lewis, D.; Pearse, E. *Lancet* 2(8044): 934; 1977.

A 67-yr-old man presented with follicular lymphoma in the transformation phase. Trypsin banding revealed a marker chromosome 14q⁺ in all abnormal mitoses examined; cells in the ascitic fluid closely resembled those of Burkitt's lymphoma. Other chromosome abnormalities, including an addition band on the q(32) position of chromosome 14 and trisomy of chromosome 7, were also present. These findings suggest that Burkitt's lymphoma cells originate from follicular B lymphocytes. (15 refs.)

77-6555 Marker Chromosome 14q⁺ in Non-endemic Burkitt's Lymphoma. (Eng.) Philip, P. (Dept. Medicine A, Rigshospitalet, Blegdamsve 9, DK-2100 Copenhagen, Denmark); Jensen, M. K.; Pallesen, G. *Cancer* 39(4): 1495-1499; 1977.

In tumor cells obtained by bone marrow aspiration from a 17-yr-old boy with non-endemic Burkitt's lymphoma, the marker chromosome 14q⁺, seen previously in endemic Burkitt's tumors, was found in 20% q cells. Other marker chromosomes were found in mitotic cells without the 14q⁺. (29 refs.)

77-6556 Atypical Surface Marker Characteristics in a T-Cell Lymphoma. (Eng) Janossy, G. (Membrane Immunology Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London, England); McVerry, B. A.; Goldstone, A. H.; Souhami, R. L.; Cawley, J. C.; Thompson, D. S. *Scand J Haematol* 19(4): 411-415; 1977.

Atypical biological characteristics in a case of T cell lymphoma in a 50-yr-old man are presented. Localized acid phosphatase, non-specific α -naphthol acid esterase activities and a convoluted nuclear membrane indicated T cell origin, but the cells did not form E rosettes and lacked surface immunoglobulin. This case indicates that study of a wide range of markers is sometimes necessary for correct classification of a lymphoma. (22 refs.)

77-6557 Variable Phenotypic Expression of an X-linked Recessive Lymphoproliferative Syndrome. (Eng) Purtilo, D. T. (Dept. Pathology, Univ. Massachusetts Medical Sch., 55 Lake Ave., N., Worcester, MA 01605); DeFlorio, D.; Hutt, L. M.; Bhawan, J.; Yang, J. P.; Otto, R.; Edwards, W. *N Engl J Med* 297(20): 1077-1081; 1977.

Investigation of a family in which four boys had cancer re-

vealed that at least 20 men had the X-linked recessive lymphoproliferative syndrome. There were a variety of phenotypes: aroliferative phenotypes consisted of aplastic anemia, agranulocytosis, or acquired hypogammaglobulinemia; proliferative phenotypes of B cells included disorders associated with Epstein-Barr virus (EBV), American Burkitt's lymphoma, immunoblastic sarcoma of B cells, fatal infectious mononucleosis, or plasmacytoma. The lymphoproliferative disorders probably arose from an immunodeficiency to EBV. The variable phenotypic expression may have reflected individual differences in viral dose, duration of exposure, and age at virus exposure. The aroliferative phenotypes, such as acquired hypogammaglobulinemia, may have resulted from excessive suppressor cell activity on B cells. The proliferative phenotypes, such as Burkitt's lymphoma or fatal infectious mononucleosis, may have resulted from infection by EBV and failure to stop the proliferation of B cells. (35 refs.)

77-6558 Chromosomal Heteromorphism in Patients with Chronic Lymphocytic Leukemia. (Spa) Prieto, F. (Laboratorio de Genetica, Clinica Infantil, Ciudad Sanitaria de la Seguridad Social, La Fe, Valencia, Spain); Badia, L.; Mayans, J.; Amigo, V.; Soler, M. A.; Marty, M. L. *Sangre* 22(5-B): 807-813; 1977.

The incidence of chromosomal heteromorphism was determined in 27 patients with chronic lymphocytic leukemia. Compared with healthy controls, paracentromeric heterochromatin was diminished in chromosomes 1 and 9 of these patients. This trait may represent a predisposition to the disease. (14 refs.)

77-6559 Genetic Selection Methods in the Fight Against Leukemia. (Rus) Karlikov, D. V. (All-Union Scientific Res. Inst. Livestock Raising, USSR); Korolev, N. I. *Veterinariia* (6): 56-59; 1977.

A total of 1,308 cows of known lineage were under systematic observation for leukemia for several years. Leukemia was detected in 109 animals belonging to 54/173 families investigated. The incidence of leukemia was 30.56% among the female offspring of leukemic mothers and 6.53% among those of healthy mothers. The findings indicate a significant relationship between mother and daughter generations in terms of leukemia morbidity, possibly by transmission of the leukemogenic agent (virus) through the placenta and/or colostrum, by direct contact, or by the transmission of genetic factors determining resistance to leukemia. Significant differences were found among the female offspring of healthy breeder bulls in terms of leukemia morbidity as well. Selection of parents with respect to the leukemia morbidity of their ancestors made it possible to reduce the leukemia morbidity in female offspring from 8% to 1%. (no refs.)

7-6560 **Leukemogenic Transformation of AKR Thymocytes incubated on Thymic Reticular Epithelial Cells (Meeting Abstract).** (Eng) Smolinsky, S. (Weizmann Inst. Science, Rehovot, Israel); Haas, M.; Cohen, I. R.; Feldman, M. *Isr J Med Sci* 13(10): 1062; 1977. (no refs.)

7-6561 **Divergent Patterns of Marrow Cell Suspension Culture Growth in the Myeloid Leukemias: Correlation of In Vitro Findings with Clinical Features.** (Eng) Elias, L. (Dept. Medicine, Div. Hematology, Stanford Univ. Sch. Medicine, Stanford, CA 94305); Greenberg, P. *Blood* 50(2): 263-274; 1977.

A study of cellular recovery, maturation, and colony-forming cell (CFC) generation of bone marrow cells from 23 patients with acute, subacute, and chronic myeloid leukemia (AML, SML, and CML) revealed an increased recovery of proliferative myeloid cells from liquid culture in 6/8 AML patients at diagnosis or relapse and 5/7 untreated SML patients. Also, AML and SML patients with rapid clinical progression showed greater recovery of cells in vitro with less maturation than patients with more stable disease. Marrow from CML patients exhibited normal myeloid maturation patterns with increased or decreased recovery of CFC. Increased numbers of myeloblasts and promyelocytes were noted in 3/4 studies. AML patients followed sequentially in apparent remission, but with impending relapse, whereas 28/32 studies made during stable remission were normal. These results indicate that in vitro culture of marrow cells has value in the clinical evaluation of patients with myeloid leukemias and in the study of factors involved in the progression of these diseases. (7 refs.)

7-6562 **A Late Clonal Evolution of a Human Leukemia Line: Sequential Cytogenetic Studies.** (Eng) Guat, A. M. (Institut de Cancerologie et d'Immunogenetique, 94800 Villejuif, France); Dutrillaux, B.; Rosenfeld, C. *Eur J Cancer* 13(2): 123-130; 1977.

The cytogenetic evolution of a cultured cell line from a patient with acute myeloid leukemia was studied for over 4 yr. After an initial diploid period, cells became heteroploid at 35 mo. At 39 mo they returned to a diploid state with some triploid cells. Distal despiralizations on chromosomes 3 and B were present in all cells by this time. (12 refs.)

7-6563 **Hodgkin's Disease Occurring During Acute Leukaemia in Remission.** (Eng) Woodruff, R. (Dept. Medical Oncology, St. Bartholomew's Hosp., London, England); Brearley, R. L.; Whitehouse, J. M.; Lister, T. A.; Stansfeld, A. G.; Malpas, J. S.; Sutcliffe, S. B.; Thompson, E. I.; Aur, R. J. *Lancet* 2(8044): 900-903; 1977.

The case reports are presented of three women, aged 18, 30, and 7 yr, who developed Hodgkin's disease while in remission from acute lymphoblastic leukemia. The reason for the development of a second neoplasm in these patients is unknown; it is possible that Hodgkin's disease developed as a result of radiotherapy and chemotherapy. (25 refs.)

77-6564 **Hodgkin's Disease Complicating Crohn's Colitis.** (Eng) Codling, B. W. (Dept. Pathology, Queen Elizabeth Hosp., Birmingham, England); Keighley, M. R.; Slaney, G. *Surgery* 82(5): 625-628; 1977.

A 35-yr-old man with a 16-yr history of Crohn's disease developed Hodgkin's disease. The bowel lesion predominated, with two hepatic tumor foci as the only manifestation of the tumor elsewhere. The finding of other patients with primary lymphoma of the gastrointestinal tract and Crohn's disease suggests an association between the two. (10 refs.)

77-6565 **A Comparative Study of Human Cell Lines Derived from Patients with Lymphoma, Leukemia, and Infectious Mononucleosis: Membrane Properties, Ultrastructure, and Surface Morphology.** (Eng) Ben-Bassat, H. (Chanock Centre Virology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Polliack, A.; Mitrani-Rosenbaum, S.; Reichert, F.; Froimovici, M.; Goldblum, N. *Cancer* 40(4): 1481-1491; 1977.

The membrane properties and ultrastructural features of lymphoid cell lines from patients with infectious mononucleosis (IM), Hodgkin's lymphoma (LB-129), African and non-African Burkitt's lymphoma (Bu-4, Raji, and DG-75), and acute lymphoblastic leukemia (Molt-4) were compared. Cells from Burkitt's lymphoma patients were spherical, had a relatively uniform morphology, showed abundant lipid droplets, and exhibited low cap-forming ability with concanavalin A (Con A). The Epstein-Barr virus (EBV) genome-negative DG-75 cells from a patient with non-African Burkitt's lymphoma were similar to Bu-4 and Raji in many respects, but they showed a high cap-forming ability. IM and LB-129 cells had a less stereotyped morphology and differed from the Burkitt's lymphoma cells in their growth characteristics, response to Con A, and ultrastructure. The cells were rounded or elongated with a 'hand mirror' shape, and they lacked multiple cytoplasmic lipid droplets typical of Burkitt's cells. Under the scanning electron microscope, most cells from these lines had varying numbers of microvilli, but the IM and LB-129 cells displayed marginal ruffles, some blebs, and rare uropods. These five cell lines were readily identified as B-lymphocytic by immunologic methods, but DG-75 cells

lacked EBV nuclear antigen and EBV receptors. The Molt 4 cells were different in all respects. They were identified as T lymphocytes and displayed relatively smooth surfaces with few microvilli. The significance of these findings is discussed, and it is suggested that differences in membrane properties may be useful in characterizing various established cultured lymphoid cells. (30 refs.)

- 77-6566 **Comparison between Membranes of Malignant and Non-Malignant Rat Colonic Epithelial Cells (Meeting Abstract).** (Eng) Barkla, D. H. (Dept. Anatomy, Monash Univ., Clayton, Vic. 3168, Australia); Tutton, P. J. *J Anat* 124(2): 518-519; 1977. (no refs.)

- 77-6567 **Biologic and Morphologic Properties of a New Ascites Cell Line Derived from a Lucke Renal Adenocarcinoma-bearing *Rana pipiens*.** (Eng) Kucera, L. S. (Dept. Microbiology and Immunology, Bowman Gray Sch. Medicine, Wake Forrest Univ., Winston-Salem, NC 27103); Leake, E. S.; Edwards, I. J.; Wright, M. J. *J Reticuloendothel Soc* 22(4): 349-362; 1977.

Ascites cells from a Lucke tumor-bearing *Rana pipiens* were isolated and characterized. Epitheliallike ascites cells were found to have many properties in common with an established Lucke tumor (LT-1) cell line and with other herpesvirus-transformed cells. Both the ascites and LT-1 cells possessed surface concanavalin A agglutinin sites. Data from immune cytotoxicity tests revealed the presence of membrane antigen(s) on ascites and LT-1 cells that was reactive with hyperimmune serum raised against natural winter-phase Lucke tumor cells. The ascites cell line exhibited morphologic characteristics distinct from those of other amphibian transformed cell lines. The ascites cells tended to grow as aggregates that later adopted an organoidlike conformation. Ultrastructurally, these cells had large cytoplasmic inclusions formed mainly by a crystalloid material of unknown origin. (18 refs.)

- 77-6568 **Neoplasia in Soft-Shell Clams (*Mya arenaria*) Collected from Oil-impacted Sites.** (Eng) Yevich, P. P. (Environmental Res. Lab., U.S. Environmental Protection Agency, Narragansett, RI 02882); Barszcz, C. A. *Ann NY Acad Sci* 298: 409-426; 1977.

Histopathologic studies were carried out on soft-shell crabs collected from two oil-spill sites in Maine (Long Cove and Harpswell Neck) from 1970 through 1975. Hematopoietic neoplasms were found in the crabs from Harpswell Neck and in some of the Long Cove crabs collected after November 1974. Before this data, the crabs at this site exhibited only gonadal neoplasms. The reason for this change in tumor type was not determined, and the oils were not implicated as the cause of neoplasm induction. The development of the neoplasms was not associated with any seasonal or cyclic change or with the size or age of the crabs. (9 refs.)

See also:

- *(Rev.): 77-6003, 77-6004, 77-6018, 77-6029, 77-6033, 77-6068, 77-6074, 77-6086, 77-6087, 77-6094, 77-6095, 77-6098, 77-6101, 77-6102, 77-6103, 77-6104, 77-6105, 77-6106, 77-6107, 77-6108, 77-6109, 77-6110, 77-6111, 77-6112, 77-6113, 77-6116, 77-6119, 77-6120.
*(Chem.): 77-6144, 77-6156, 77-6186, 77-6188, 77-6189, 77-6195, 77-6215, 77-6219, 77-6229, 77-6230, 77-6237, 77-6238, 77-6243, 77-6244, 77-6245, 77-6246, 77-6248, 77-6249, 77-6251, 77-6252, 77-6261, 77-6262, 77-6263, 77-6265, 77-6266, 77-6270, 77-6271, 77-6272, 77-6279, 77-6290, 77-6291, 77-6292.
*(Viral): 77-6341, 77-6346, 77-6352, 77-6365, 77-6370, 77-6384, 77-6399, 77-6404, 77-6412, 77-6413, 77-6414, 77-6415, 77-6416, 77-6417, 77-6418, 77-6419, 77-6420, 77-6421, 77-6422, 77-6423, 77-6424, 77-6425, 77-6426, 77-6427, 77-6428, 77-6429, 77-6430, 77-6431, 77-6432, 77-6433, 77-6434, 77-6435, 77-6436, 77-6437, 77-6438, 77-6439, 77-6440, 77-6441, 77-6442, 77-6443, 77-6444, 77-6445, 77-6446, 77-6447, 77-6448, 77-6449, 77-6450, 77-6451, 77-6452, 77-6453, 77-6454, 77-6455, 77-6456, 77-6457, 77-6458, 77-6459, 77-6460, 77-6461, 77-6462, 77-6463, 77-6464, 77-6465, 77-6466, 77-6467, 77-6468, 77-6469, 77-6470, 77-6471, 77-6472, 77-6473, 77-6474, 77-6475, 77-6476, 77-6477, 77-6478, 77-6479, 77-6480, 77-6481, 77-6482, 77-6483, 77-6484, 77-6485, 77-6486, 77-6487, 77-6488, 77-6489, 77-6490, 77-6491, 77-6492, 77-6493, 77-6494, 77-6495, 77-6496, 77-6497, 77-6498, 77-6499, 77-6500, 77-6501, 77-6502, 77-6503, 77-6504, 77-6505, 77-6506, 77-6507, 77-6508, 77-6509, 77-6510, 77-6511, 77-6512, 77-6513, 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EPIDEMIOLOGY AND BIOMETRY

7-6569 **Geographic Distribution of Cancers of the Digestive Tract in Belgium: Unequal Distribution of Mortality due to Cancers of the Stomach and of the Rectum.** (Fre.) Ramioul, L. (Ecole de Sante Publique de l'Universite Libre de Bruxelles, Laboratoire d'Epidemiologie et de Medecine sociale, Rue Belliard 100, B-1040 Brussels, Belgium); Tuyns, A. J. *Acta Gastroenterol Belg* 40(3-4): 129-147; 1977.

An analysis of mortality data for cancer of the digestive tract in Belgium from 1961 to 1962 and 1969 to 1971 revealed that death from stomach and rectal cancer was significantly higher during both these time periods in the Flemish region compared with the Wallon provinces. However, mortality from cancer of the esophagus and intestine was similar throughout the country. The mortality from cancer of the esophagus was similar to that in France. The high rate of stomach cancer in the Flemish provinces approximated that in the Netherlands and West Germany; the lower rate in the Wallon provinces was similar to that in France. The role of dietary habits, alcohol, and tobacco consumption in these different areas is emphasized, and a closer epidemiological study is recommended. (34 refs.)

7-6570 **High School Contact among Persons with Leukemia and Lymphoma.** (Eng) Zack, M. M. Chronic Diseases Div., Bureau Epidemiology, Center Disease Control, Public Health Service, U.S. Dept. Health, Education and Welfare, Atlanta, GA 30333; Heath, C. W.; Andrews, M. D.; Grivas, A. S.; Christine, B. W. *J Natl Cancer Inst* 59(5): 1343-1349; 1977.

To investigate the role of interpersonal contact in the etiology of leukemia and lymphoma, patterns of contact among Connecticut high school students were examined in relation to all forms of leukemia and lymphoma. The Connecticut Tumor Registry was the source of all cases of leukemia and lymphoma among residents 15-29 yr old diagnosed from 1960 through 1971. The study group comprised 421 subjects, 29 with Hodgkin's disease (HD), 71 with non-HD lymphoma, and 101 with leukemia. The risk of having attended the same grade at the same school during the same year was greater among students with HD than among controls (relative risk, 1.44; approx 95% lower confidence limit, 1.05). The risk of developing HD was also greater among students enrolled simultaneously at the same school as students already diagnosed with HD than among students not so enrolled (relative risk, 2.05; 95% lower confidence limit, 1.39). However, fewer HD cases (16) were diagnosed from 1965 through 1970 at schools that formerly had patients enrolled (1959-64)

than at matched schools without these patients (24). These results suggest that there were increased levels of high school contact among HD patients. However, this conclusion should be viewed with caution, as controls were generated on a theoretical basis, and actual personal contacts were not determined. No significant case linkage occurred in non-HD lymphoma or leukemia cases, although the number of cases was limited. Increased contact was noted between HD and non-HD lymphomas (relative risk, 1.41; approx 95% lower confidence limit, 1.11). (23 refs.)

77-6571 **Familial Cancer in the General Population.** (Eng) Albert, S. (Michigan Cancer Foundation, 110 E. Warren, Detroit, MI 48201); Child, M. *Cancer* 40(4): 1674-1679; 1977.

Since 1971, in the course of collecting human milk samples from lactating women for NCI, their family histories were also assembled. Ages, causes of death, reproductive histories, and data on cancer occurrence were obtained for all first-degree relatives of 2,411 white probands. A total of 2,098 cancers were identified in 31,945 persons. The cancers were confirmed by pathology reports, hospital and doctors' records, or death certificates. Of the family lineages (ie, first-degree relatives), 65.9% had no cancers and 8.0% had two or more. For all cancers taken together, clustering was not significant, but there were significantly more observed than expected cancers in lineages with cancer of breast, ovary, skin, corpus uteri, stomach, rectum, lung and bronchus, or colon. Little or no excess was observed in lineages with leukemia, lymphoma, and cancer of the cervix or prostate. The relative risk of breast cancer was increased 1.5 times for daughters and 3.8 times for sisters of women with the disease. (19 refs.)

77-6572 **Carcinoma of the Cervix: Present Status and Future.** (Eng) Marcial, V. A. (Radiation Oncology Div., Puerto Rico Nuclear Center, Caparra Heights Station, San Juan, Puerto Rico 00935). *Cancer* 39(2): 945-958; 1977.

The current magnitude of the problem of cervical carcinoma in the continental US and Puerto Rico, areas with different socioeconomic levels, is discussed. The incidence of invasive carcinoma of the cervix is decreasing in both areas because of improvements in socioeconomic conditions and adequate utilization of the Pap smear. Although the US experienced > 50% reduction in the incidence rate during 1947-1969,

cervical carcinoma is still a significant problem, with an estimated 20,000 new cases in 1976. Mortality from cervical carcinoma has been reduced 60% in the last 20 yr. This is related to reduction in the incidence of the invasive forms of the disease, earlier diagnosis, and improvements in therapy. The yield in terms of survival and disease-free status in the pelvis is high for early stages of the disease (90% 5-yr survival and 97% control of pelvic tumor for Stage I), but Stages IIIB and IV show a failure rate of $\geq 50\%$ in the irradiated volume and a high incidence of metastases to the para-aortic, lung and abdominal viscera. (71 refs.)

- 77-6573 **Differences in Breast Cancer Between Japan and the United States.** (Eng) Nemoto, T. (Dept. Breast Surgery, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263); Tominaga, T.; Chamberlain, A.; Iwasa, Z.; Koyama, H.; Hama, M.; Bross, I.; Dao, T. *J Natl Cancer Inst* 58(2): 193-197; 1977.

The overall survival and recurrence-free survival rates for breast cancer were compared in 375 Japanese women (JW) treated by radical or modified radical mastectomy, and 352 American women (AW) treated by radical mastectomy. The JW were younger (median age, 46 yr) than the AW (median age, 55.5 yr). A higher proportion of AW had metastases in more than four nodes; in general, breast cancer in JW tended to metastasize to axillary nodes less often and less extensively than it did in the AW. Furthermore, JW with involvement of more than four nodes had much better recurrence-free survival rates. This could not be attributed to lesser node involvement, as the median number of involved nodes was 7.5 for both groups. The overall 5-yr recurrence rate was the same for both groups, so that the JW did not have a prolonged metastasis-free period. This would seem to indicate that the better recurrence-free survival rates in JW were the result of more patients being cured of cancer and not of a delay of metastases in those who developed them. Overall survival was better for JW, although the difference was not as great as that for recurrence-free survival. When survivals of patients with metastases from time of metastases till death were compared in 82 JW and 189 AW, survival of the latter was significantly better. This offsets the differences in the recurrence-free survival rates. JW of menopausal age (40 to 54 yr) had better recurrence-free survival rates than the other age groups. This age advantage was not observed in AW. Thus, there are biologic differences of breast cancer between JW and AW with regard to recurrence-free survival rates, overall survival, and tendency to metastasize. (9 refs.)

- 77-6574 **Histologic and Epidemiologic Features of Breast Cancer (Meeting Abstract).** (Eng.) Vakil, D. V. (Faculty Medicine, Univ. Toronto, Toronto, Ontario,

Canada M5S 1A8). *Am J Epidemiol* 106(3): 249; 1977. (no refs.)

- 77-6575 **Trends in Breast Cancer Incidence in a Population Based Registry (1953-1975) (Meeting Abstract).** (Eng.) Gaudette, L. A. (Alberta Cancer Hosp. Board, Edmonton, Alberta, Canada T6G 1Z2); Burns, P. E.; Lees, A. W.; Grace, M. *Am J Epidemiol* 106(3): 249; 1977. (no refs.)

- 77-6576 **Cell Proliferation Kinetics in Gynecologic Cancer.** (Eng.) Siracky, J. (Cancer Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia); Matoska, J.; Siracka, E. *Neoplasma* 24(3): 327-332; 1977.

The cell proliferation kinetics of gynecologic cancers of different anatomic sites, both primary and metastatic, and of the corresponding normal tissue of the host were analyzed. The results indicate that in spite of the similar morphologic and histologic characteristics of the cancers at each particular site, cytokinetic data can vary widely, depending on the proliferative capacity of the tissues, proportion of proliferating and nonproliferating cells, and extent of cell loss. Use of a double-labeling (^{14}C -TdR/ ^3H -TdR) method in vitro revealed that, in general, there was a prolongation of DNA synthesis in the tumor cell population (to between 20 and 30 hr), compared with the duration of DNA synthesis in normal tissue (between 10 and 15 hr). (16 refs.)

- 77-6577 **A Mortality Study among Workers in an English Asbestos Factory.** (Eng.) Peto, J. (DHSS Cancer Epidemiology and Clinical Trials Unit, Dept. Regius Professor Medicine, Univ. Oxford, Oxford, England); Doll, R.; Howard, S. V.; Kinlen, L. J.; Lewinsohn, H. C. *Br J Ind Med* 34(3): 169-173; 1977.

A study was made of 1,106 men and women who had worked for > 10 yr in dust risk areas of an asbestos textile factory. The object of this study was to establish the value of technical improvements since 1931. Since there is a delay of 15 or more years between first exposure and any resulting cancer, the results do not reflect the effects of working conditions over the last 15-20 yr. Workers first exposed before 1933 suffered a marked excess of lung cancer and respiratory disease; there was also some excess mortality from lung cancer and mesothelioma and respiratory disease in those who entered the dust risk areas after January 1, 1933. There have been few deaths among those first exposed in 1951 or thereafter, but there still appears to be an excess of deaths from lung cancer 15 or more years after first exposure (5 observed, 1.8 expected). The numbers are too small, however, for the magnitude of the excess of lung cancer in those first employed after 1950 to be estimated with precision. (9 refs.)

77-6578 **Insulation Workers in Belfast. A Further Study of Mortality due to Asbestos Exposure (1940-1975).** (Eng.) Elmes, P. C. (Dept. Therapeutics and Pharmacology, Queen's Univ. Belfast, Belfast, BT9 7BL, Ireland); Thompson, M. J. *Br J Ind Med* 34(3): 174-180; 1977.

The fate of the survivors and mortality of 162 asbestos insulation workers were studied over the period 1940-1975. In 1940, the men ranged in age from 16 to 66 yr and some had already worked for up to 35 yr (mean 11.3 yr). By the end of 1975 there were only 40 survivors out of an expected 108. Until 1965, there had been an overall excess of deaths due to asbestosis with or without tuberculosis, gastrointestinal cancer, bronchial carcinoma, and mesothelioma. From 1965 onward, the overall death rate of the workers was not so excessive, but there was still a marked excess of deaths from bronchial cancer and mesothelioma. This study indicates that exposure of this sort carries a significant risk of bronchial cancer even when asbestosis is no longer a significant direct cause of death. (6 refs.)

77-6579 **Nasal Cancers, Symptoms and Upper Airway Function in Woodworkers.** (Eng.) Andersen, H. (Hygiejnisk Institut, Universitetsparken, DK 8000 Aarhus Denmark); Andersen, I.; Solgaard, J. *Br J Ind Med* 34(3): 211-207; 1977.

Hospital case records and field measurements in furniture industries were investigated to determine the incidence of various types of nasal cancer in relation to occupation. Results show that in 186 cases of nasal cancer diagnosed between 1965 and 1974, in a population of 2.0 million, 114/157 nodermal tumors were found in men. Adenocarcinoma occurred in 17 patients (2 women, 15 men), 12 of whom had a history of occupational exposure to wood dust in the furniture industry. The latent period ranged from 28 to 57 yr. Among the remaining 99 tumors in men, there was occupational exposure to wood dust in 10. Dust concentrations affecting 43 of the 68 workers studied were $> 5 \text{ mg/m}^3$. Middle ear inflammation and common colds were more frequent at high dust concentrations, and the number of workers with nasal mucostasis was directly proportional to the wood dust concentration. It is suggested that the mucostatic factor in wood dust is of significance in the development of nasal adenocarcinoma in furniture workers because of the prolonged retention of wood dust in the nasal cavity. (15 refs.)

77-6580 **Nasal Cancer among Woodworkers in the US (Meeting Abstract).** (Eng.) Brinton, L. A. (Environmental Epidemiology Branch, NCI, Bethesda, MD 20014); Blot, W. J.; Stone, B. J.; Fraumeni, J. F. *Am J Epidemiol* 106(3): 231; 1977. (no refs.)

77-6581 **Nickel Carcinogenesis of the Respiratory Tract.** (Eng.) Barton, R. T. (Univ. California Cancer Center AL-423, Los Angeles, CA 90024). *J Otolaryngol* 6(5): 412-422; 1977.

There is a high incidence of cancer of the nose and sinuses (28 times the expected rate) among Norwegian nickel workers. The efforts of the nickel industry to minimize the risk of nickel carcinogenesis, the surgical aspects of nickel-related nose and sinus neoplasms, and the clinical significance of the specific mutagenic theory of chemical carcinogenesis are discussed. (41 refs.)

77-6582 **A Mortality Study of Coke Oven Workers in Two South Wales Integrated Steelworks.** (Eng.) Davies, G. M. (British Steel Corporation, Welsh Lab. and Strip Mill Products, Port Talbot, Glamorgan, Wales). *Br J Ind Med* 34(4): 291-297; 1977.

The standardized mortality ratios for malignant neoplasms, cardiovascular disease, respiratory disease, and other diseases were calculated for 610 coke oven workers (82 deaths) at two steelworks. There were 26 malignant neoplasms against 23.47 expected; the difference was not significant. (22 refs.)

77-6583 **A Case-Control Study of Bladder Cancer in the Rubber Industry (Meeting Abstract).** (Eng.) Checkoway, H. (Occupational Health Studies Group, Chapel Hill, NC 27514); Arp, E.; Holbrook, R. H.; Jones, F. S.; McMichael, A. J.; Monson, R.; Smith, A. H.; Tyroler, H. A.; Van Ert, M. *Am J Epidemiol* 106(3): 243; 1977. (no refs.)

77-6584 **Association of Cancer Mortality Rates and Trihalomethane Levels in Municipal Drinking Water Supplies (Meeting Abstract).** (Eng.) Cantor, K. P. (NCI, Bethesda, MD 20014); Hoover, R.; Mason, T.; McCabe, L. J. *Am J Epidemiol* 106(3): 230-231; 1977. (no refs.)

77-6585 **Identification and Distribution of Inorganic Components in Water: What to Measure?** (Eng.) Glass, G. E. (Environmental Res. Lab., U. S. Environmental Protection Agency, Duluth, MN 55804). *Ann NY Acad Sci* 298: 31-46; 1977.

The chemical equilibria model was used to calculate the molecular distribution of inorganic components in Lake Superior water. This distribution was compared with effects on aquatic organisms such as the water flea (*Daphnea magna*).

Nitilotriacetate and EDTA were found to dominate the aquo chemistry of Cu and Cd, but not Hg. Metals introduced to water as silicate mineral particles contributed little to the total metal tissue content in fish. Analysis of the drinking water in Duluth showed wide variations in Pb, Cl₂, NH₃, asbestiform fibers, hexafluorosilicic acid, and glass contents at different locations and times. (52 refs.)

77-6586 Systematic Collaborative Studies on Neoplasms in Marine Animals as Related to the Environment. (Eng) Stich, H. F. (Cancer Res. Centre, Univ. British Columbia, Vancouver, British Columbia, Canada); Acton, A. B.; Oishi, K.; Yamazaki, F.; Harada, T.; Hibino, T.; Moser, H. G. *Ann NY Acad Sci* 298: 374-388; 1977.

Data are presented on the global distributions of skin papillomas among flatfish species, on local differences in tumor prevalence, and on yearly and seasonal variations in prevalence. The geographic pattern of these tumors should provide an opportunity to examine the interaction between a possible viral panepidemic and chemical carcinogens or cocarcinogens. The possible use of flatfish for monitoring changes in the marine environment is also discussed. (40 refs.)

77-6587 Fish Disease in the Bering Sea. (Eng) Wellings, S. R. (Dept. Pathology, Sch. Medicine, Univ. California at Davis, Davis, CA 95616); Alpers, C. E.; McCain, B. B.; Myers, M. S. *Ann NY Acad Sci* 298: 290-304; 1977.

In September and October of 1975, 30,000 demersal fish of 25 species were caught at various stations in the Bering Sea and examined for neoplastic disease. Epidermal papillomas occurred in 1% of rock sole, tumors of the pseudobranchial gland occurred in 7.4% of Pacific Cod, and lymphocystis disease occurred in 2.1% of yellowfin sole examined. The viral etiology of these diseases is discussed. (20 refs.)

See also:

- *(Rev.): 77-6015, 77-6016, 77-6017, 77-6019, 77-6020, 77-6021, 77-6022, 77-6023, 77-6024, 77-6025, 77-6026, 77-6027, 77-6028, 77-6029, 77-6030, 77-6031, 77-6033, 77-6059, 77-6064, 77-6071, 77-6072, 77-6076, 77-6080, 77-6081, 77-6094, 77-6113, 77-6114, 77-6115, 77-6116, 77-6117, 77-6118, 77-6119, 77-6120, 77-6121, 77-6122, 77-6123, 77-6124, 77-6125, 77-6126, 77-6127.
 *(Chem.): 77-6151, 77-6163, 77-6183, 77-6200, 77-6221, 77-6223, 77-6228, 77-6231, 77-6237, 77-6296.
 *(Phys.): 77-6300, 77-6302, 77-6304.
 *(Viral): 77-6403.
 *(Path.): 77-6505, 77-6521, 77-6540, 77-6568.

MISCELLANEOUS

77-6588 Intracellular Protein Degradation in Growing, in Density-inhibited, and in Serum-restricted Fibroblast Cultures. (Eng) Hendil, K. B. (August Krogh Inst., Univ. Copenhagen, 13, Universitetsparken, DK 2100, Copenhagen 0, Denmark). *J Cell Physiol* 92(9): 353-364; 1977.

Intracellular protein degradation rates were examined in growing, density-inhibited, and serum-restricted fibroblast cultures. Exponentially growing BALB/3T3 mouse fibroblasts contain protein populations with slow and fast turnover. The degradation rate of both stability classes of protein was increased in cultures whose growth was inhibited by a high cell density. Serum deprivation, which halted cell growth, also accelerated protein breakdown. Protein degradation in SV3T3 cells (a simian virus 40-transformed derivative of BALB/3T3) was not influenced by a high culture density but was increased by serum deprivation. Cyclic nucleotides had no effect on protein degradation, and cycloheximide inhibited protein degradation to a variable extent. (41 refs.)

77-6589 Characterization of Human Malignant Melanoma Cell Lines. VII. Glycoprotein Synthesis and Shedding as Revealed by [³H]Glucosamine Labeling. (Eng) Rahman, A. F. (Dept. Pediatrics, 4H17, McMaster Univ., Hamilton, Ontario L8S 4J9, Canada); Liao, S. K.; Dent, P. B. *In Vitro* 13(9): 580-585; 1977.

Glycoprotein synthesis and shedding of macromolecules were examined in the malignant melanoma cell line CaCL 73-36 (M₂) with the use of ³H-glucosamine. Culture of cells in medium containing 0.125 to 5.0 μ Ci of glucosamine revealed that cell-associated radioactivity increased as a function of isotope concentration from 3.8% to 18.0%; nonspecific binding of label in the medium remained constant at approx 1%. In all subsequent studies, 0.5 μ Ci/ml glucosamine was used. Addition of glucose to fresh and exhausted medium reduced glucosamine uptake by 56.2% and 88%, respectively. Pulse-labeling in fresh medium revealed that max uptake occurred during logarithmic growth at 48 hr. Release of labeled cell-surface macromolecules was proportional to the concentration of added trypsin (10, 50, or 100 μ g/ml), with a max release of 16.0% occurring in cultures exposed to trypsin in situ. Higher concentrations of trypsin did not release more label. Spontaneous release of labeled macromolecules was linear, and a peak of > 50% was reached at 96 hr. The percentage of trypsin-releasable radioactivity was not affected by pulsing. It is suggested that purified human neoplastic cells may be a source of antigen for immunological studies. (15 refs.)

77-6590 Cellular Growth Control: Properties of a Unique Adhering Derivative of L5178Y Cells. (Eng) Gersten, D. M. (Basic Res. Program, Frederick Cancer Res. Center, Frederick, MD 21701); Hakimi, J.; Bosmann, H. B. *Biochem Biophys Res Commun* 74(3): 1014-1022; 1977.

A new cell line, L5178Y Adh, derived from L5178Y lymphoma cells is described. The new cells grow both in suspension and attached to a substratum but not in contact with each other. Either cell subline can give rise to the other. Kinetic and size analyses suggest that the factor determining which cells settle out from the inoculum and which cells attach to the substratum is the cell volume or density. Once cells attach to the substratum, they grow with kinetics similar to those of the parent line (a suspension culture). The less-dense (cells which remain suspended) have a rapid doubling time (8-9 hr) and eventually outgrow the adhering cells. Cells that attach to the substratum ultimately undergo a morphologic differentiation not seen in the suspended population. This work demonstrates a cell line with a remarkable ability to react to its environment in terms of growth control, and it illustrates the heterogeneity of a malignant cell population. (9 refs.)

77-6591 Inhibition of Growth of Normal Murine Granulocytes by Cocultured Acute Leukemic Cells. (Eng) Miller, A. M. (Dept. Medicine, Beth Israel Hosp., 330 Brookline Ave., Boston, MA 02215); Page, P. L.; Hartwell, B. L.; Robinson, S. H. *Blood* 50(5): 799-809; 1977.

Coculture of equal numbers of C1498 murine acute myelogenous leukemia cells and normal mouse bone marrow cells in diffusion chambers (DC) completely suppressed normal granulocyte development within a few days. Suppression of granulopoiesis was not observed with radiation-killed leukemic cells. Direct interaction between the leukemic and normal cells appears to be necessary, since there was no inhibition when the two populations were separated by an intervening Millipore filter in double-DC cultures. When the ratio of leukemic to normal cells was reduced from 50/50 to 15/85, granulocytic cell proliferation remained normal for a longer time but eventually ceased. With both the 15/85 and 50/50 cultures, the ratio of leukemic to normal granulocytic cells rose to approx the same level, 6/1-7/1, just before granulopoiesis was suppressed. In both instances, macrophage numbers were similar to those in control cultures of normal marrow cells alone. When mixtures of leukemic and normal bone marrow cells were assayed by the agar and spleen colony-forming techniques, rather than by culture in DC, formation of colony-forming cells in vitro was unaltered but formation of normal, differentiated spleen colony-forming cells was

markedly reduced. This suggests that the leukemic cells exert their inhibitory influence at the level of the pluripotential hemopoietic stem cell. The mixed DC cultures of leukemic and normal marrow cells may provide an experimental model for elucidating the mechanisms by which human leukemia subverts normal hemopoiesis. (19 refs.)

- 77-6592 Stimulation of Sterol and DNA Synthesis in Leukemic Blood Cells by Low Concentrations of Phytohemagglutinin.** (Eng) Chen, H. W. (Jackson Lab., Bar Harbor, ME 04609); Heiniger, H. J.; Kandutsch, A. A. *Exp Cell Res* 109(5): 253-262; 1977.

The response of leukemic cells from AKR/J mice to phytohemagglutinin (PHA) was compared with that of normal lymphocytes. PHA first stimulated cholesterol synthesis and then DNA synthesis in both lymphocytes and leukemic cells. The neoplastic cells were, however, much more sensitive to PHA, requiring less time and a lower concentration of the lectin for optimum stimulation as compared with lymphocytes. In fact, the amount of PHA required to activate lymphocytes to proliferate, as measured by increases in sterol and DNA synthesis, was inhibitory to leukemic cells. Treatment with 25-hydroxycholesterol and 7-ketocholesterol depressed the basal level of cholesterol synthesis and the induction of cholesterol synthesis following PHA in lymphocytes and leukemic cells. These two oxygenated derivatives of cholesterol are known to be potent and specific inhibitors of sterol synthesis. Blockage of sterol synthesis by these reagents also abolished PHA-activated DNA synthesis in lymphocytes and leukemic cells. The results support the hypothesis that cholesterol synthesis is an important event leading to cell proliferation. (38 refs.)

- 77-6593 Analysis of Gene Expression in Regenerating Rat Liver by Hybridization of Nuclear and Cytoplasmic RNA with DNA.** (Eng) Greene, R. F. (Dept. Anatomy, Medical Coll. Pennsylvania, Philadelphia, PA); Fausto, N. *Cancer Res* 37(1): 118-127; 1977.

DNA-RNA hybridization-saturation and RNA-depletion experiments were performed to determine whether massive gene activation occurs in rat liver following partial hepatectomy. RNA was extracted from the whole cells, nuclei, post-mitochondrial extracts, and polysomes from livers of normal, sham-operated, or partially hepatectomized male albino rats. The purified RNA was labeled with ³H-dimethyl sulfate in vitro and hybridized with nuclear DNA under conditions in which only repetitive sequence transcripts form hybrids with DNA. There were no differences in the saturation levels of whole-cell RNA or nuclear RNA (nRNA) from the three animal groups. Cytoplasmic RNA from 6-hr regenerating livers saturated the DNA at a much lower concentration than that required for RNA from normal or sham-operated rats.

On the other hand, the concentration of nRNA from 6-hr regenerating livers necessary to saturate DNA was slightly higher than that of nRNA from normal liver. This was confirmed in experiments using nRNA labeled in vivo. These results suggest that for repetitive sequence transcripts, massive derepression of the genome does not occur in the early stages of liver regeneration. The alterations detected primarily reflect changes in RNA concentration rather than alterations in gene expression. (43 refs.)

- 77-6594 Studies of Human Histone Messenger RNA. I. Methods for the Isolation and Partial Characterization of RNA Fractions Containing Human Histone from HeLa S3 Polyribosomes.** (Eng) Stephens, R. E. (Wistar Inst. Anatomy and Biology, Philadelphia, PA 19104); Pan, C. J.; Ajiro, K.; Dolby, T. W.; Borun, T. W. *J Biol Chem* 252(1): 166-172; 1977.

Large quantities of nonpolyadenylated [poly(A-)] 4S to 18S RNA were isolated from the polyribosomes of S-phase HeLa S3 cells and fractionated into multiple discrete RNA components by continuous elution preparative electrophoresis. Previous studies have shown that treatment of S-phase HeLa cells with cytosine arabinoside inhibits DNA replication and causes translatable histone messenger RNA (mRNA) species to disappear from cytoplasmic polyribosomes. In the present study, cytosine arabinoside did not appreciably affect the major 7.5S to 8S RNA species, but it did cause the disappearance of 8.6S to 13S RNA components from preparative electrophoresis elution profiles of S-phase polyribosomal 4S to 18S RNA. Base ratio analysis of the 8.6S to 13S putative histone mRNA species indicates that they are GC-rich but unlike the HeLa 18S or 28S S ribosomal RNA in base composition. (22 refs.)

- 77-6595 Comparison of Contact-mediated Communication in Normal and Transformed Human Cells in Culture.** (Eng) Corsaro, C. M. (Dept. Medical Genetics, Univ. Toronto, Toronto, Ontario, Canada M5S 1A8); Muehlestein, B. R. *Proc Natl Acad Sci USA* 74(10): 4476-4480; 1977.

Differences in contact-mediated communication between normal and transformed human cells in culture were detected by an assay that quantitates the transfer of 6-thioguanine acid from hypoxanthine phosphoribosyltransferase-positive donor cells to negative recipient cells through gap junctions. Cells cultured from human tumors and simian virus 40-transformed cells were compared with the normal human fibroblasts from which they were derived with gap junction-deficient L cells. The communication, which is extensive in normal cells, is significantly reduced when transformed cells

are used as either donors or recipients in the contact-feeding assay. Furthermore, the reduction in the transfer of nucleotides is enhanced when transformed cells are used as both donors and recipients, indicating a dosage effect or synergism independent of enzyme activity. Fetal cells have a contact-feeding phenotype intermediate between that of normal and transformed cells. It is suggested that the decrease in communication of nucleotides in transformed cells reflects quantitative or qualitative changes in membrane components responsible for gap junction formation. (38 refs.)

- 7-6596 **Patterns of Plasminogen Activator Production in Cultured Normal Embryonic Cells.** (Eng) Rohrich, S. T. (Rockefeller Univ., New York, NY 10021); Rifkin, D. B. *J Cell Biol* 75(1): 31-42; 1977.

Cultured normal low-passage embryo fibroblasts (mouse, rat, hamster, chicken, and human) and two untransformed A31 clones of a BALB/3T3 line were studied for production of plasminogen activator (PA). All normal embryonic cells had barely detectable PA levels at low density. All but the chicken and hamster cells developed increasingly higher PA levels as they approached and attained confluence; they gradually lost some or all of the activity after confluence. A study of rat embryo fibroblasts and C57BL/6 mouse cells and their transformed counterparts showed that the normal cells had peak PA levels below those of the transformants. In BALB 3T3 cells, the peak level of PA was three times higher than that of low-passage mouse cells, and it remained high indefinitely beyond confluence. In mouse embryo fibroblasts, both the cell-associated and secreted PA levels in normal cells varied as a function of cell density and they reached their peak at confluence. Cell-associated inhibitors of fibrinolysis were not responsible for the observed PA activity. PA production depended on the metabolic activity of the normal cells, such that serum supplementation and growth phase directly influenced the level of PA. The observed PA increase in the absence of serum probably results from increased production and not from adsorption of secreted PA. The decrease of PA upon serum-readdition represented repression of PA, probably by a non-acid-labile protease inhibitor. (33 refs.)

- 7-6597 **Direction of Locomotion in Clones of Non-neoplastic Fibroblasts and Their Neoplastic Derivatives.** (Eng) Sanford, K. K. (Cell Physiology and Oncogenesis Section, Biochemistry Lab., NCI, NIH, Bethesda, MD 20014); Jones, G. M.; Tarone, R. E.; Fox, C. H. *Exp Cell Res* 109(2): 454-459; 1977.

The locomotion of neoplastic cloned mouse fibroblasts and their spontaneously transformed derivatives was compared by cinematomicrography. The spontaneous transformants grew as invasive transplantable sarcomas. The non-neoplastic

cells failed to grow as tumors, and did not show the characteristic morphologic alterations, growth in soft agar, or susceptibility to killing by activated macrophages demonstrated by transformed cells. The nonneoplastic cells tended to maintain the same direction of locomotion in sequential 2.5 hr periods but the neoplastic cells had a random pattern of locomotion. No relationship between cell density and randomness of locomotion was observed. The nonneoplastic cells appeared to grow as rapidly as the neoplastic cells. However, the neoplastic cells had higher locomotion rates possibly associated with their invasive potential in vivo. A reduced amount of lamellar cytoplasm in the neoplastic cells and the high migration rate may account for their random pattern of locomotion. (28 refs.)

- 77-6598 **The Migration Ability of Transformed Fibroblast-like Cells Grown on Substrate with Ordered Relief (Quantitative Estimation).** (Eng.) Slavnaia, I. L. (Lab. Mechanisms Carcinogenesis, Oncological Res. Center, USSR Acad. Med. Sciences, Moscow, USSR); Rovenskii, Iu. A. *Tsitologiya* 19(9): 1011-1017; 1977.

The migration ability of 11 transformed mouse, rat, hamster and human fibroblast-like cell lines cultured on a substratum with grooves 5 to 40 μ meter deep was examined. A reduction or total absence of migration ability was noted for most of these lines, as compared to normal embryonic cells. A greater reduction was noted in mouse and rat than in human cells. In the hamster lines, transformed and embryonic cells showed an equally weak migration response. (14 refs.)

- 77-6599 **Age-associated Changes in Tumorigenic Cells from a Murine Fibrosarcoma (Meeting Abstract).** (Eng) Finlay-Jones, J. J. (Univ. Dept. Microbiology, Perth Medical Centre, Univ. Western Australia, Nedland, W. A. 6009); Sheridan, J. W. *Clin Exp Pharmacol Physiol* 4(5): 483; 1977. (no refs.)

- 77-6600 **Molecular Weight Effects of Polylysine on Film Sarcoma Yield (Meeting Abstract).** (Eng) Lavelle, S. M. (Dept. Experimental Medicine, Univ. Coll., Galway, Ireland); MacIomhair, M.. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p.77; 1977. (no refs.)

Author Index

- Aaronson, S. A., 77-6315, 77-6343
 Abanobi, S. E., 77-6254
 Abdine, H., 77-6185
 Abidi, S., 77-6184
 Abildgaard, C. F., 77-6513
 Acton, A. B., 77-6586
 Adams, S. L., 77-6313
 Adelstein, R. S., 77-6421
 Ades, E. W., 77-6436
 Agarwal, R. A., 77-6247
 Ahmed, F. E., 77-6303
 Aisenberg, A. C., 77-6488
 Ajiro, K., 77-6594
 Al-Hindawi, A. Y., 77-6226
 Albert, R. E., 77-6020
 Albert, S., 77-6571
 Alekhin, R. M., 77-6087
 Alena, B., 77-6403
 Alexander, P., 77-6445
 Alexandrov, K., 77-6213
 Alfieri, A., 77-6454
 Allaben, W. T., 77-6242
 Allen, J. R., 77-6156
 Alm, G. V., 77-6353
 Alpers, C. E., 77-6587
 Alpers, J., 77-6446
 Althoff, J., 77-6248
 Altman, N. H., 77-6164
 Alvarez San Cristobal, A., 77-6074
 Alwine, J. C., 77-6420
 Amigo, V., 77-6558
 Amos, D. B., 77-6437
 Andersen, H. C., 77-6579
 Andersen, I., 77-6579
 Anderson, E., 77-6020
 Anderson, G. R., 77-6367
 Anderson, J. L., 77-6421, 77-6542
 Andersson-Anvret, M., 77-6404
 Andrews, A. W., 77-6297
 Andrews, M. D., 77-6570
 Andrianova, M. M., 77-6102
 Annegers, J. F., 77-6231
 Anonymous, 77-6059
 Aoki, K., 77-6143
 Appel, K. E., 77-6251, 77-6258
 Appella, E., 77-6427, 77-6490
 Arcement, L. J., 77-6357
 Archer, M. C., 77-6065
 Arfellini, G., 77-6293
 Arkhangelskaia, A. V., 77-6210
 Armuth, V., 77-6135
 Arnoux, B., 77-6510
 Aroche-Alfonso, R. M., 77-6176
 Aronoff, B. L., 77-6237
 Arp, E., 77-6583
 Asker, R. L., 77-6181
 Assa, R., 77-6232
 Atkin, N. B., 77-6527
 Aufses, A. H., 77-6531
 Aur, R. J., 77-6563
 Auriol, M., 77-6542
 Autrup, H., 77-6212, 77-6298
 Bacchetti, S., 77-6089
 Bacigalupo, A., 77-6103
 Badia, L., 77-6558
 Badr, F. M., 77-6181
 Badr, R. S., 77-6181
 Baker, H. W., 77-6237
 Balazs, M., 77-6238
 Ballantyne, A. J., 77-6183
 Baltimore, D., 77-6323
 Baluda, M. A., 77-6309, 77-6311
 Bargheon, J., 77-6122
 Barkla, D. H., 77-6171, 77-6566
 Barnes, A. B., 77-6029
 Barnstable, C., 77-6096
 Barrington, M. H., 77-6196
 Barszcz, C. A., 77-6568
 Bartholomew, J. C., 77-6340
 Barton, R. T., 77-6581
 Batsakis, J. G., 77-6535
 Bauer, H., 77-6481
 Baumler, A., 77-6494
 Beaudreau, G. S., 77-6318
 Bedouelle, H., 77-6225
 Beemon, K., 77-6314, 77-6364
 Beesau, O., 77-6159
 Belitskii, G. A., 77-6011
 Ben-Bassat, H., 77-6565
 Bend, J. R., 77-6158
 Bendas, C. M., 77-6339
 Benfield, J. R., 77-6215
 Benford, D. J., 77-6148
 Bensilum, S., 77-6187
 Bensky, N. D., 77-6464
 Berenblum, I., 77-6135
 Berezina, L. K., 77-6326
 Berger, A. E., 77-6437
 Bern, H. A., 77-6529
 Berzinski, R., 77-6371
 Bhawan, J., 77-6557
 Bhisey, R. A., 77-6144
 Bianciffiori, C., 77-6528
 Bichler, K. H., 77-6138
 Billeter, M. A., 77-6322
 Binns, R., 77-6190, 77-6191
 Birg, F., 77-6379
 Birkenmeier, E., 77-6425
 Bischoff, F., 77-6037
 Bishop, J. M., 77-6376
 Bister, K., 77-6330
 Bjarnason, O., 77-6540
 Bjorkholm, M., 77-6473
 Black, E. G., 77-6226
 Black, P. H., 77-6464
 Blagorodov, S. G., 77-6210
 Blaineau, C., 77-6349
 Blanc, F., 77-6160
 Blasecki, J. W., 77-6448
 Bloch-Shtacher, N., 77-6553
 Bloomfield, C. D., 77-6471
 Blot, W. J., 77-6124, 77-6580
 Blumer, M., 77-6200
 Blumer, W., 77-6200
 Bock, F. G., 77-6010
 Boeryd, B., 77-6451
 Boesel, R. W., 77-6112
 Bogdanov, G. I., 77-6522
 Bogovskii, B. P., 77-6351
 Bolognesi, D. P., 77-6319
 Bolt, H. M., 77-6157
 Bonerandi, J. J., 77-6546
 Bonney, R. J., 77-6289
 Boot, L. M., 77-6235
 Borun, T. W., 77-6594
 Borzsonyi, M., 77-6269, 77-6274
 Bosmann, H. B., 77-6590
 Boulanger, P., 77-6389
 Boutwell, R. K., 77-6079
 Boyd, P. R., 77-6244
 Brada, Z., 77-6164
 Brady, J. N., 77-6381
 Brahic, M., 77-6333
 Brand, I., 77-6497
 Brand, K. G., 77-6497
 Brearley, R. L., 77-6563
 Brehant, J., 77-6521
 Brewer, D. B., 77-6226
 Bridges, J. W., 77-6148
 Briggs, M., 77-6038
 Brightwell, J., 77-6224
 Briles, W. E., 77-6327
 Brill, E., 77-6147, 77-6286
 Brinton, L. A., 77-6580
 Broker, T. R., 77-6392, 77-6392
 Bross, I., 77-6573
 Brown, C. C., 77-6260
 Brown, J. M., 77-6083
 Brown, J. P., 77-6179
 Brown, R. J., 77-6179
 Brown, T. D., 77-6410
 Brugge, J. S., 77-6312
 Bruszewski, J., 77-6414
 Bryan, G. T., 77-6003
 Bryson, G., 77-6037
 Bubenikova, D., 77-6301
 Bucci, L., 77-6117
 Bucheler, J., 77-6276
 Buck, M., 77-6170
 Buening, M. K., 77-6180
 Bulba, S., 77-6164
 Bulbrook, R. D., 77-6531
 Bundeally, A. E., 77-6174
 Buoen, L. C., 77-6497
 Burckhart, M. F., 77-6216
 Burke, M. D., 77-6148, 77-6204
 Burns, F. J., 77-6305
 Burns, P. E., 77-6575
 Burny, A., 77-6319
 Buttignol, M., 77-6221
 Cabradilla, C. D., 77-6343
 Calnek, B. W., 77-6328
 Calop, J., 77-6216
 Campa, M., 77-6458
 Camus, D., 77-6469
 Cantor, K. P., 77-6584
 Canuto, R. A., 77-6259
 Capel, I. D., 77-6182
 Capen, C. C., 77-6365

- Capron, A., 77-6469
 Caputo, T. A., 77-6031
 Carcassonne, Y., 77-6489
 Carlson, D. M., 77-6129
 Carruthers, C., 77-6494
 Carter, R. F., 77-6224
 Carter, R. L., 77-6458
 Cascales, C., 77-6133
 Cascales, M., 77-6133
 Cassingena, R., 77-6415
 Castleden, W. M., 77-6169
 Castro, A. E., 77-6332
 Catovsky, D., 77-6554
 Cawley, J. C., 77-6556
 Celen, P., 77-6320
 Celma, M. L., 77-6417
 Chadha, K. C., 77-6398
 Chamberlain, A., 77-6573
 Champ, M., 77-6063
 Chan, H., 77-6551
 Chan, P. C., 77-6234
 Chang, C., 77-6542
 Chang, E. H., 77-6361, 77-6363
 Chang, J. P., 77-6515
 Chang, R. L., 77-6209
 Chang, S. K., 77-6254
 Chantrenne, H., 77-6319
 Charles, E. H., 77-6524
 Chartrand, S., 77-6471
 Chatterjee, S. K., 77-6480
 Checkoway, H., 77-6583
 Chedid, A., 77-6174
 Chen, H. W., 77-6592
 Chen, S. Y., 77-6519, 77-6545
 Chi, J. G., 77-6548
 Child, M., 77-6571
 Chirigos, M. A., 77-6197
 Chizh, G. I., 77-6512
 Chlopkiwicz, B., 77-6294
 Chomette, G., 77-6542
 Chow, L. T., 77-6392, 77-6392
 Chrestian, M. A., 77-6546
 Chretien, J., 77-6510
 Christine, B. W., 77-6570
 Churg, J., 77-6073
 Cicurel, L., 77-6441
 Cinader, B., 77-6097
 Claesson, M. H., 77-6468
 Clancy, R., 77-6446
 Clark, D. G., 77-6186
 Clark, S., 77-6268
 Clark, T. D., 77-6359
 Claude, J. R., 77-6160
 Cleuter, Y., 77-6319
 Coccia, P. F., 77-6471
 Codling, B. W., 77-6564
 Cogen, B., 77-6377
 Coggin, J. H., 77-6493
 Cohen, A., 77-6432
 Cohen, A. H., 77-6215
 Cohen, I. R., 77-6560
 Colcher, D., 77-6374
 Coleman, D. V., 77-6385
 Collett, M. S., 77-6321
 Colwell, R. R., 77-6296
 Condori, J., 77-6524
 Conliffe, M., 77-6491
 Conney, A. H., 77-6180, 77-6202
 77-6209
 Connors, M. H., 77-6513
 Consigli, R. A., 77-6381
 Corsaro, C. M., 77-6595
 Corte, J., 77-6471
 Costa, J., 77-6383
 Cotic, L., 77-6369
 Cowgill, U. M., 77-6152
 Cowie, C. H., 77-6359
 Craven, P. A., 77-6273
 Croce, C. M., 77-6441
 Crowell, R. L., 77-6339
 Cudkowicz, G., 77-6450
 Cutler, S. J., 77-6115
 Dahlberg, J. E., 77-6323
 Dahlgren, M. E., 77-6289
 Daiker, K. C., 77-6201
 Dallaire, G., 77-6027
 Danes, B. S., 77-6506
 Danetskaia, E. V., 77-6299
 Daniel, J. W., 77-6187
 Daniel, M. D., 77-6413
 Daniel, R. A., 77-6385
 Danna, K. J., 77-6416
 Dannenberg, A. M., 77-6017
 Danon, D., 77-6466
 Dansette, P. M., 77-6207, 77-6213
 Dao, T., 77-6573
 Dao, T. L., 77-6203
 Das, S. K., 77-6544
 Dastoor, M. N., 77-6309
 Daudel, R., 77-6008
 Daune, M. P., 77-6137
 Dausset, J., 77-6094
 Davies, G. M., 77-6582
 Davies, J. N., 77-6126
 Davies, P., 77-6289
 Davis, F. M., 77-6391
 Davnichenko, L. S., 77-6278
 Dawe, C. J., 77-6023
 de Crombrughe, B., 77-6313
 de Faire, U., 77-6473
 De Ianni, L., 77-6117, 77-6118
 De Recondo, A. M., 77-6424
 de Vogel, N., 77-6281
 DeBoer, D. J., 77-6440
 Declève, A., 77-6345
 Decloitre, F., 77-6205
 DeFlorio, D., 77-6557
 Delaforge, N., 77-6146
 DeLap, R. J., 77-6386
 Delchier, J. C., 77-6068
 Demchenko, A. P., 77-6476
 Dent, P. B., 77-6589
 Derache, R., 77-6066
 DeRubertis, F. R., 77-6273
 Dessaint, J. P., 77-6469
 Desser-Wiest, L., 77-6236
 Devos, R., 77-6320
 Dhar, A., 77-6388
 Dhar, R., 77-6417
 Di Maro, L., 77-6525
 Di Mayorca, G., 77-6382
 Dietrich, P. S., 77-6179
 Dikshtein, E. A., 77-6523
 Dina, D., 77-6364
 Dinnen, J. S., 77-6539
 Dion, A. S., 77-6373
 Dipaolo, J. A., 77-6272
 Diringer, H., 77-6310
 DiSciullo, S. O., 77-6439
 Doerfler, W., 77-6390
 Dolby, T. W., 77-6594
 Dolken, G., 77-6409
 Doll, R., 77-6577
 Dolphin, G. W., 77-6078
 Doniach, I., 77-6540
 Donner, L., 77-6402
 Dooling, E. C., 77-6548
 Dor, P., 77-6543
 Dorange, J. L., 77-6067, 77-6146
 Dorfman, S. M., 77-6512
 Dostal, V., 77-6487
 Dove, L., 77-6491
 Doyle, T., 77-6352, 77-6354
 Drill, V. A., 77-6036
 Dubbs, D. R., 77-6397, 77-6402
 Ducluzeau, R., 77-6063
 Duesberg, P. H., 77-6330
 Dupuy-Coin, A. M., 77-6400
 Dutrillaux, B., 77-6562
 Dvorak, A. M., 77-6464
 Dvorak, H. F., 77-6464
 Dvorak, V., 77-6301
 Dyas, B. J., 77-6191
 Dyson, P., 77-6163
 Ebbin, A. J., 77-6552
 Eckhart, W., 77-6377
 Edwards, I. J., 77-6567
 Edwards, W., 77-6557
 Egami, N., 77-6249
 El Aasser, A. B., 77-6266
 El Merzabani, M., 77-6266
 Elias, L., 77-6561
 Elliott, E. V., 77-6477
 Elmes, P. C., 77-6578
 Elsebai, I., 77-6266
 Eltze, M., 77-6253
 Emmelot, P., 77-6250
 Emminger, E., 77-6270
 Engel, E., 77-6106
 Entwistle, K. W., 77-6517
 Epstein, M. A., 77-6406
 Epstein, S. S., 77-6277
 Erikson, R. L., 77-6312
 Eskola, J., 77-6452
 Esra, G., 77-6414
 Estrade, S., 77-6415
 Evans, W. C., 77-6062
 Fabricant, J., 77-6328
 Falk, J. A., 77-6447
 Falk, R. E., 77-6447
 Faller, D. V., 77-6344
 Fanning, E., 77-6390
 Faras, A. J., 77-6321
 Farrow, G. M., 77-6260
 Fasske, E., 77-6341
 Fausto, N., 77-6593
 Favaloro, J., 77-6379
 Favre, R., 77-6489

Fawell, J. K., 77-6186
 Feczko, P. J., 77-6504
 Feijoo, B., 77-6133
 Feldman, M., 77-6560
 Felix, H., 77-6279
 Felton, J. S., 77-6018
 Fergie, R. C., 77-6194
 Feron, V. J., 77-6214
 Field, A. M., 77-6385
 Fiers, W., 77-6320
 Filipe, M. I., 77-6502
 Filippi, P., 77-6333
 Fillmore, J. L., 77-6223
 Finerty, S., 77-6406
 Finlay-Jones, J. J., 77-6599
 Finogenova, M. A., 77-6102
 Fischer, E., 77-6469
 Fishbein, L., 77-6076
 Flaks, B., 77-6136
 Flamm, W. G., 77-6019
 Flavell, A. J., 77-6380
 Flippen, J. H., 77-6100
 Flodrops, M., 77-6213
 Fong, C. K., 77-6090
 Fontanges, R., 77-6216
 Ford, W. L., 77-6470
 Forney, J. P., 77-6030
 Forni, G., 77-6092
 Forsby, N., 77-6404
 Fortner, J. G., 77-6180
 Fowler, B. A., 77-6014
 Fowler, E. F., 77-6460
 Fox, C. H., 77-6597
 Frank, A., 77-6407
 Frank, F. R., 77-6453
 Frank, P. H., 77-6504
 Fraumeni, J. F., 77-6228, 77-6580
 Frayssinet, C., 77-6213
 Friedman, R. J., 77-6491
 Friedman, R. M., 77-6361, 77-6363
 77-6375
 Friis, R. R., 77-6310
 Froberg, H., 77-6001
 Froimovici, M., 77-6565
 Fuchs, G., 77-6084
 Fuchs, R. P., 77-6137
 Fugaro, S., 77-6212, 77-6298
 Fujinaga, K., 77-6395
 Fukuhisa, K., 77-6302
 Fukumoto, Y., 77-6387
 Furst, A., 77-6220
 Gajl-Peczalska, K. J., 77-6471
 Gak, J. C., 77-6283
 Gallipoli, A., 77-6117, 77-6118
 Gallo, R. C., 77-6370
 Gambarelli, D., 77-6546
 Garcea, R., 77-6259
 Garcia, C. R., 77-6036
 Gard, D. A., 77-6518
 Gardner, E. J., 77-6506
 Gardner, M. B., 77-6414
 Gardner, S. D., 77-6385
 Garnier, H., 77-6542
 Gass, G. H., 77-6242
 Gastpar, H., 77-6549
 Gattozzi, C., 77-6463

Gaudette, L. A., 77-6575
 Gavora, J. S., 77-6482
 Gedigk, P., 77-6271
 Gelfant, S., 77-6128
 Gelinas, R. E., 77-6392, 77-6392
 Jenkins, G., 77-6531
 Genovesi, E. V., 77-6356
 Gerber, D. A., 77-6077
 Gerber, P., 77-6413
 Gergely, R., 77-6238
 Gericke, D., 77-6138, 77-6153
 Gerner, E. W., 77-6304
 Gersten, D. M., 77-6590
 Gerstner, H. B., 77-6050
 Getty, S. M., 77-6015
 Ghysdael, J., 77-6319
 Gibson, J. P., 77-6241
 Gibson, P. E., 77-6385
 Gilden, R. V., 77-6371
 Gilles, F. H., 77-6548
 Gillis, E., 77-6320
 Gilmour, D. G., 77-6467
 Ginsberg, H. S., 77-6394
 Giordana, M. T., 77-6002
 Gipson, T. G., 77-6491
 Girard, M., 77-6424
 Gisselbrecht, S., 77-6349
 Glass, G. B., 77-6098
 Glass, G. E., 77-6585
 Glaudemans, C. P., 77-6475
 Goguel, A. F., 77-6459
 Gol-Winkler, R., 77-6256
 Gola, R., 77-6546
 Goldberg, R. J., 77-6339
 Goldblum, N., 77-6565
 Golde, D. W., 77-6511
 Goldenberg, D. M., 77-6503
 Goldstein, L. T., 77-6455
 Goldstone, A. H., 77-6556
 Goldzieher, J. W., 77-6035
 Gomatos, P. J., 77-6347
 Gonda, M. A., 77-6508
 Goodman, D. G., 77-6260
 Gordon, D. S., 77-6435
 Gordon, J., 77-6036
 Gordon, S. W., 77-6520
 Gori, G. B., 77-6123
 Gough, T. A., 77-6266
 Goutier, R., 77-6256
 Grace, M., 77-6575
 Graevskaia, N. A., 77-6324
 Graham, F. L., 77-6089
 Graillot, C., 77-6283
 Grandgenett, D. P., 77-6321
 Grandjean, C., 77-6248
 Grant, C. K., 77-6440
 Grauballe, P. C., 77-6401
 Gray, L. A., 77-6228
 Gray, L. G., 77-6359
 Green, I., 77-6092, 77-6336
 Green, S., 77-6292
 Greenberg, P., 77-6561
 Greene, R. F., 77-6593
 Greenman, D. L., 77-6034
 Greenwald, P., 77-6031
 Greenwood, R. H., 77-6539

Griffin, G. F., 77-6196
 Griffiths, S. G., 77-6226
 Grivas, A. S., 77-6570
 Grosjean, D., 77-6199
 Grotzsch, H., 77-6138
 Grubbs, C. J., 77-6260
 Gruss, P., 77-6419
 Guida, A., 77-6525
 Guillebaud, J., 77-6032
 Gullino, P. M., 77-6111
 Gunven, P., 77-6438
 Guschchina, E. A., 77-6326
 Gushchin, B. V., 77-6326
 Gutter, B., 77-6306
 Haas, M., 77-6560
 Haase, A. T., 77-6333
 Hadjiolov, D., 77-6254
 Hadler, H. I., 77-6165
 Haemmerli, G., 77-6279
 Haga, M., 77-6173
 Hahn, E. W., 77-6454
 Hakimi, J., 77-6590
 Hall, J. D., 77-6431
 Haller, O., 77-6450
 Halsted, C. C., 77-6513
 Hama, M., 77-6573
 Hammond, M. E., 77-6464
 Hanafusa, H., 77-6316
 Handa, H., 77-6396
 Hanson, C. A., 77-6315
 Harada, F., 77-6323
 Harada, T., 77-6387, 77-6586
 Haran-Ghera, N., 77-6346
 Hardy, R., 77-6025
 Hardy, S. B., 77-6518
 Hardy, W. D., 77-6331
 Harrington, G. W., 77-6254
 Harris, C. C., 77-6212, 77-6298
 Hartley, J. W., 77-6350
 Hartman, J. R., 77-6422
 Hartwell, B. L., 77-6591
 Harvey, R. G., 77-6208
 Harwick, R. D., 77-6519, 77-6545
 Harzmann, R., 77-6138
 Haseltine, W. A., 77-6323
 Hashizume, T., 77-6302
 Haslam, S. Z., 77-6529
 Hassoun, J., 77-6546
 Hawkes, S. P., 77-6340
 Hayami, M., 77-6481
 Hayes, A. W., 77-6175
 Hays, E. F., 77-6354
 Hayward, W. S., 77-6316
 Heath, C. W., 77-6570
 Hecker, E., 77-6053
 Heilmann, L. J., 77-6318
 Heiniger, H. J., 77-6592
 Helson, C., 77-6544
 Helson, C. L., 77-6544
 Helton, E. D., 77-6035
 Hemmingsen, H., 77-6443
 Henderson, B. E., 77-6403
 Henderson, E., 77-6407
 Hendil, K. B., 77-6588
 Henle, W., 77-6404, 77-6412
 Hennache, B., 77-6389

- Henschler, D., 77-6039
Heppleston, A. G., 77-6163
Herberman, R. B., 77-6434, 77-6486
Herman, T. M., 77-6318
Hermann, M., 77-6225
Hersey, P., 77-6485
Heywood, P., 77-6391
Heywood, R., 77-6239
Hibbs, J. B., 77-6462
Hibino, T., 77-6586
Hicks, R. M., 77-6266
Higgins, N. P., 77-6005
Higginson, J., 77-6113, 77-6114
Highman, B., 77-6229
Hill, P., 77-6233
Hill, R. N., 77-6155
Hirono, I., 77-6173, 77-6177
Hisanaga, A., 77-6222
Ho, J. H., 77-6120
Ho-Terry, L., 77-6432
Hobson, W. C., 77-6227
Hochman, P. S., 77-6450
Hodge, L. D., 77-6391
Hoffenberg, R., 77-6226
Hoffman, D. J., 77-6217
Hoffman, M. K., 77-6449
Hoffmann, D., 77-6168, 77-6168
77-6184
Hofnung, M., 77-6225
Holbrook, R. H., 77-6583
Holden, A. V., 77-6025
Holden, H. T., 77-6486
Holm, G., 77-6473
Hoover, E. A., 77-6331
Hoover, R., 77-6228, 77-6584
Hopkins, N., 77-6344
Hopkins, R. H., 77-6508
Howard, B. H., 77-6313
Howard, D. K., 77-6374
Howard, S. V., 77-6577
Hsiung, G. D., 77-6090, 77-6091
Hsu, W. T., 77-6208
Hu, C. P., 77-6092
Huang, P. H., 77-6257
Hubert, E., 77-6319
Hubert-Habart, M., 77-6159
Huez, G., 77-6319
Huff, J. E., 77-6050
Huffman, K. W., 77-6241
Hunig, T., 77-6484
Hunter, T., 77-6314
Hurot, M. A., 77-6349
Hussain, F. H., 77-6181
Hutt, L. M., 77-6557
Hutton, J. J., 77-6198, 77-6198
Hyde, E., 77-6167
IARC Working Group, 77-6040
77-6041, 77-6042, 77-6043, 77-6044
77-6045, 77-6046, 77-6047, 77-6048
77-6049, 77-6051, 77-6052, 77-6054
77-6055, 77-6056, 77-6057
Ignjatovic, J., 77-6481
Iguchi, T., 77-6230
Ikawa, Y., 77-6317
Ikeda, R. M., 77-6513
Ikenaga, M., 77-6288
Imbert, J., 77-6161
Indo, K., 77-6195
Infante, P. F., 77-6145
Ing, R., 77-6120
Ioannides, C., 77-6150
Iqbal, Z. M., 77-6277
Isaki, L., 77-6296
Isbister, J., 77-6296
Ishikawa, T., 77-6526
Ishimoto, A., 77-6350
Ishinishi, N., 77-6222
Itoh, M., 77-6472
Iverson, F., 77-6282
Iwasa, Z., 77-6573
Jackisch, R., 77-6253
Jacob, S. T., 77-6132
Jamasbi, R. J., 77-6492
Janiaud, P., 77-6146
Janossy, G., 77-6556
Jarrett, W. F., 77-6178
Jensen, M. K., 77-6555
Jerina, D. M., 77-6202, 77-6207
77-6209
Jernstrom, B., 77-6204
Jing, J. S., 77-6403
Johansson, K., 77-6393
Johnson, D. W., 77-6332
Johnson, K. H., 77-6497
Johnston, R., 77-6025
Johnston, W. D., 77-6183
Jondal, M., 77-6438
Jones, F. S., 77-6583
Jones, G. M., 77-6597
Jones, J. H., 77-6539
Jones, L., 77-6096
Jones, R., 77-6070
Jortay, A. M., 77-6543
Jung, A., 77-6253
Kagan, E., 77-6465
Kahan, B. D., 77-6503
Kakunaga, T., 77-6288
Kalter, S. S., 77-6413
Kambic, V., 77-6243
Kamen, R., 77-6379, 77-6380
Kandutsch, A. A., 77-6592
Kannerstein, M., 77-6073
Kapitulnik, J., 77-6180
Kaplan, H. S., 77-6345
Karlikov, D. V., 77-6559
Karran, P., 77-6005
Karshin, W. L., 77-6357
Kask, A., 77-6092
Kato, H., 77-6399
Kato, K., 77-6173, 77-6177, 77-6426
Kato, T., 77-6173, 77-6177
Keighley, M. R., 77-6564
Keller, R., 77-6461
Kersey, J. H., 77-6471
Ketkar, M. B., 77-6189, 77-6211
Ketterer, B., 77-6142
Kettmann, R., 77-6319
Khafagy, M., 77-6454
Kiessling, R., 77-6450
Kim, U., 77-6480
Kingsbury, D. T., 77-6398
Kinlen, L. J., 77-6125, 77-6577
Kit, S., 77-6397, 77-6402
Klauber, M. R., 77-6223
Kleihues, P., 77-6276
Klein, D., 77-6063
Klein, G., 77-6404, 77-6408, 77-6409
77-6410, 77-6411
Kleinerman, J., 77-6463
Klimenko, S. M., 77-6326
Knipscher, R. C., 77-6336
Knyszynski, A., 77-6466
Kobori, O., 77-6271
Kodama, T., 77-6387
Kodama, Y., 77-6222
Kofler, K., 77-6533
Kofranek, V., 77-6301
Kolb, H., 77-6478
Kolodin, V. I., 77-6280
Komuro, M., 77-6342
Kondrat'ev, Iu. S., 77-6278
Konen, T., 77-6092
Kornfeld, P., 77-6531
Korolev, N. I., 77-6559
Kosuge, T., 77-6141
Kotaskova, Z., 77-6301
Koyama, H., 77-6573
Koziorowska, J., 77-6294
Kozlova, I. N., 77-6102
Kozyrev, Iu. A., 77-6087
Krush, A. J., 77-6506
Kruysse, A., 77-6214
Kucera, L. S., 77-6567
Kuechenthal, I., 77-6347
Kunz, W., 77-6251, 77-6258
Kunze, E., 77-6261, 77-6262
Kurchak, M., 77-6397
Kurland, L. T., 77-6231
Kurliandskii, B. A., 77-6013
Kyono, Y., 77-6249
Ladds, P. W., 77-6517
Lafferty, K. J., 77-6443
Laib, R. J., 77-6157
Laktionov, A. M., 77-6087
Lalich, J. J., 77-6156
Lamm, S. H., 77-6145
Landolfo, S., 77-6486
Lang, M. C., 77-6137
Lankin, V. Z., 77-6210
Larsen, S. H., 77-6335
Laux, D. C., 77-6439
Lavelle, S. M., 77-6600
Lavialle, C., 77-6415
Lavrent'ev, L. N., 77-6299
Law, L. W., 77-6427, 77-6490
Leake, E. S., 77-6567
Leatherland, J. F., 77-6537
Lecointe, P., 77-6206
Lees, A. W., 77-6575
Leffell, M. S., 77-6493
Leifer, C., 77-6545
Lemay, P., 77-6348
Leon-Cazares, J. M., 77-6176
Leonard, T. B., 77-6132
Lerner, K. G., 77-6246
Lerner, R. A., 77-6196
Lesca, P., 77-6206
Levan, A., 77-6107

- Levan, G., 77-6107
 Levi, P., 77-6146
 Levin, B., 77-6504
 Levin, M. L., 77-6116
 Levin, W., 77-6202, 77-6209
 Levine, A. J., 77-6431
 Levis, A. G., 77-6221
 Levitt, M., 77-6254
 Levitt, R. C., 77-6018
 Levshin, V. F., 77-6119
 Levy, R. L., 77-6196
 Lewinsohn, H. C., 77-6577
 Lewis, D., 77-6554
 Lezhneva, O. M., 77-6351
 Li, L. H., 77-6359
 Liao, S. K., 77-6589
 Libansky, J., 77-6104
 Lieberman, M., 77-6345
 Liechty, R. D., 77-6541
 Lijinsky, W., 77-6270
 Likhachev, A. Ia., 77-6280
 Lilja, H. S., 77-6167
 Lin, E. J., 77-6208
 Lindahl, T., 77-6411
 Lindstrom, E., 77-6290
 Lingg, R. D., 77-6154
 Linkhart, S., 77-6354
 Linne, T., 77-6394
 Liotta, L. A., 77-6463
 Lippincott, J. A., 77-6131
 Lister, T. A., 77-6563
 Livstone, E. M., 77-6170
 Lloyd, D. C., 77-6078
 Lock, S., 77-6162
 Loeser, E., 77-6218
 Loiseau, P., 77-6060
 Lonai, P., 77-6346
 Long, C. W., 77-6366, 77-6371
 Long, J. C., 77-6488
 Longenecker, B. M., 77-6482
 Longhin, P. P., 77-6259
 Longnecker, D. S., 77-6166, 77-6167
 Lopez, L., 77-6443
 Lord, M. W., 77-6021
 Lorke, D., 77-6218
 Lotlikar, P. D., 77-6254
 Louie, E. W., 77-6403
 Luftig, R. B., 77-6358
 Luginbuhl, H., 77-6290
 Lugton, W. G., 77-6191
 Luka, J., 77-6411
 Lundholm, U., 77-6394
 Lvov, D. K., 77-6326
 Lyon, J. L., 77-6223
 MacDonald, P. C., 77-6030
 MacDonald, W. E., 77-6286
 MacGillivray, A. J., 77-6410
 Mach, O., 77-6311
 MacIomhair, M., 77-6600
 MacLeod, R., 77-6361, 77-6361
 MacMahon, B., 77-6120
 Magee, P. N., 77-6009
 Mah, H. D., 77-6202
 Malins, D. C., 77-6024
 Malpas, J. S., 77-6563
 Mancini, P., 77-6391
 Marbaix, G., 77-6319
 Marcial, V. A., 77-6572
 Maric, N., 77-6292
 Mark, G. J., 77-6244
 Mark, W., 77-6405
 Markovits, P., 77-6159
 Marmont, A. M., 77-6103
 Martin, R. G., 77-6542
 Martin, R. R., 77-6192, 77-6193
 Martin, W. J., 77-6491
 Marty, M. L., 77-6558
 Maruyama, T., 77-6302
 Marx, P. A., 77-6356
 Mason, T., 77-6584
 Masse, R., 77-6510
 Mate, U., 77-6240
 Matejovsky, Z., 77-6498
 Matoska, J., 77-6576
 Matovcik, L. M., 77-6367
 Matsudaira, H., 77-6143
 Matsumura, K., 77-6215
 Matsushima, M., 77-6139, 77-6140
 Maurer, L. H., 77-6509
 May, E., 77-6425
 Mayans, J., 77-6558
 Mayr, W. R., 77-6487
 Mazurenko, N. P., 77-6329
 McCabe, L. J., 77-6022, 77-6584
 McCain, B. B., 77-6587
 McCarthy, W. H., 77-6485
 McCaughey, W. T., 77-6073
 McCommas, M., 77-6296
 McCullough, B., 77-6112
 McGibbon, W. H., 77-6327
 McGinty, L., 77-6081
 McLemore, T. L., 77-6193
 McMichael, A. J., 77-6583
 McVerry, B. A., 77-6556
 Mechali, M., 77-6424
 Medeiros, E., 77-6354, 77-6376
 Meijers, M., 77-6281
 Melewicz, F. M., 77-6435, 77-6436
 Mellstedt, H., 77-6473
 Mendenhall, C. L., 77-6174
 Merezko, V. A., 77-6523
 Metcalf, D., 77-6468
 Metzler, M., 77-6227
 Meyer, G., 77-6489
 Michie, W., 77-6540
 Migeon, B. R., 77-6595
 Migita, S., 77-6479
 Mike, V., 77-6108
 Mikhailov, E. A., 77-6501
 Mikol, Y., 77-6205
 Miller, A. M., 77-6591
 Miller, A. S., 77-6545
 Miller, G., 77-6407
 Miller, G. H., 77-6071
 Miller, K., 77-6465
 Mischke, T. M., 77-6199
 Mischutin, V., 77-6151
 Mitelman, F., 77-6107
 Mitrani-Rosenbaum, S., 77-6565
 Mittal, A., 77-6388
 Mizuta, M., 77-6387
 Mohr, U., 77-6189, 77-6263, 77-6264
 77-6270
 Moller, P. C., 77-6515
 Monson, R., 77-6583
 Montesano, R., 77-6069
 Monti-Bragadin, C., 77-6369
 Moon, R. C., 77-6260
 Moore, G. E., 77-6534
 Mora, P. T., 77-6542
 Moran, D. M., 77-6359
 More, N. S., 77-6336
 Morgan, G., 77-6485
 Morgan, R. T., 77-6534
 Mori, H., 77-6173, 77-6177
 Morii, S., 77-6372
 Moroni, C., 77-6495
 Morris, A. G., 77-6415
 Morris, V. L., 77-6376
 Moser, H. G., 77-6586
 Motoi, M., 77-6334
 Mozzillo, N., 77-6117, 77-6118
 Mueller, K. W., 77-6165
 Muir, C. S., 77-6114
 Muller, W., 77-6227
 Mulvihill, M., 77-6531
 Munson, J. W., 77-6185
 Murakami, T., 77-6110
 Muranyi-Kovacs, I., 77-6161, 77-6232
 Murphy, G. P., 77-6237
 Murthy, K. K., 77-6328
 Muscoplat, C. C., 77-6332
 Musella, S., 77-6118
 Myers, M. S., 77-6587
 Myers, M. W., 77-6361
 Nadasdi, L., 77-6269
 Nagasawa, H., 77-6372
 Nagata, T., 77-6500
 Nagayo, T., 77-6499
 Nakabayashi, H., 77-6516
 Nanni, P., 77-6293
 Napalkov, N. P., 77-6280
 Naso, R. B., 77-6357
 Natarajan, A. T., 77-6281
 Nathans, D., 77-6335
 Natori, T., 77-6490
 Natsu-ume-Sakai, S., 77-6479
 Nauciel, C., 77-6459
 Nayak, N. C., 77-6388
 Naylor, B., 77-6074
 Nebert, D. W., 77-6018
 Neilson, A., 77-6494
 Neiman, I. M., 77-6102
 Nelson-Rees, W. A., 77-6414
 Nemoto, T., 77-6573
 Nesbit, M. E., 77-6471
 Nettesheim, P., 77-6492
 Neubauer, R. H., 77-6414, 77-6508
 Nevzorova, N. I., 77-6013
 Newberne, J. W., 77-6241
 Newberne, P. M., 77-6241
 Newsome, W. H., 77-6282
 Nishizawa, K., 77-6302
 Nishizuka, Y., 77-6245
 Nitchuk, M., 77-6112
 Niyogi, S. K., 77-6217
 Nobutomo, K., 77-6222

- Noda, K., 77-6387
 Noronha, R. F., 77-6255
 Norvell, M. J., 77-6229
 Nossal, N., 77-6447
 Notake, K., 77-6496
 Noterman, J., 77-6543
 Noval, J. J., 77-6457
 Novick, M., 77-6518
 Nowell, P. C., 77-6105
 Nowinski, R. C., 77-6352, 77-6354
 Nunn, M. E., 77-6434
 O'Fallon, W., 77-6231
 Obando, H., 77-6457
 Oesch, F., 77-6061
 Offringa, O. R., 77-6239
 Ogawa, K., 77-6334
 Ohmori, H., 77-6334
 Ohno, S., 77-6411, 77-6479
 Ohta, T., 77-6141
 Oishi, K., 77-6586
 Ojima, S., 77-6395
 Okamoto, T., 77-6141
 Okazaki, W., 77-6467
 Okita, K., 77-6387
 Okita, M., 77-6215
 Olden, K., 77-6313
 Olsen, R. G., 77-6331
 Olson, H. M., 77-6365
 Orgogozo, J. M., 77-6060
 Orlando, M. M., 77-6018
 Orrenius, S., 77-6204
 Oskarsson, M. K., 77-6366
 Otto, R., 77-6557
 Owada, M., 77-6317
 Owen, L. W., 77-6075
 Oyasu, R., 77-6503
 Padieu, P., 77-6146
 Page, P. L., 77-6591
 Palcic, B., 77-6369
 Palladino, M. A., 77-6444
 Pallesen, G., 77-6555
 Palmenberg, A., 77-6322
 Palopoli, F. P., 77-6241
 Pan, C. J., 77-6594
 Pan, J., 77-6417
 Panet, A., 77-6323
 Pangalis, G. A., 77-6474
 Paoletti, C., 77-6206
 Papadia, L., 77-6525
 Papadopoulo, D., 77-6159
 Papatestas, A. E., 77-6531
 Park, J. Y., 77-6434
 Parke, D. V., 77-6148, 77-6150
 Parr, I. B., 77-6445
 Pastan, I., 77-6307, 77-6313
 Patil, K., 77-6168, 77-6168
 Patiutko, Iu. I., 77-6501
 Paul, P. S., 77-6332
 Pazderka, F., 77-6482
 Pearse, E., 77-6554
 Pecar, S., 77-6369
 Pecevski, J., 77-6292
 Pena, C. E., 77-6547
 Pentreath, R. J., 77-6025
 Perocco, P., 77-6293
 Peters, G., 77-6323
 Petersen, E. E., 77-6088
 Peterson, W. D., 77-6413
 Peto, J., 77-6577
 Petrakis, N. L., 77-6120
 Petrella, G., 77-6117, 77-6118
 Pettengill, O. S., 77-6509
 Pettersson, U., 77-6393
 Philip, P., 77-6555
 Philipson, L., 77-6393
 Phillips, D. J., 77-6436
 Piaggio, G., 77-6103
 Pickel, K., 77-6449
 Pickering, R., 77-6354
 Pickthall, V. J., 77-6527
 Pietrzyk, J. J., 77-6095
 Pinter, A., 77-6269, 77-6274
 Pitot, H. C., 77-6004
 Pittman, S., 77-6554
 Pitts, J. N., 77-6199
 Pluquet de Temmerman, N., 77-6348
 Polakova, K., 77-6325
 Polderman, J., 77-6028
 Polednak, A. P., 77-6300
 Poli, G., 77-6259
 Politzer, P., 77-6201
 Pollack, R., 77-6421, 77-6431
 Polliack, A., 77-6565
 Polyakov, V. M., 77-6210
 Pomenti, A. A., 77-6373
 Pomeroy, K. A., 77-6332
 Ponten, J., 77-6308
 Poole, D., 77-6199
 Popescu, N. C., 77-6272
 Popovic, M., 77-6308, 77-6311
 Popp, J. A., 77-6254
 Poppers, P. J., 77-6180
 Portetelle, D., 77-6319
 Poston, J. W., 77-6075
 Pour, P., 77-6248, 77-6263
 Pouyssegur, J., 77-6307
 Povysil, C., 77-6498
 Pozo, F., 77-6349
 Prat, J., 77-6029
 Pratt, C. B., 77-6551
 Price, M. R., 77-6456
 Price, P. J., 77-6197
 Prieto, F., 77-6558
 Prives, C., 77-6422
 Prodi, G., 77-6293
 Provan, D., 77-6268
 Purchase, H. G., 77-6467
 Purtilo, D. T., 77-6557
 Putman, D. L., 77-6337
 Quan, S. G., 77-6511
 Quinn, L. A., 77-6534
 Rabin, H., 77-6414, 77-6508
 Rabson, A. S., 77-6383
 Radman, M., 77-6007
 Radomski, J. L., 77-6147, 77-6286
 Radsel, Z., 77-6243
 Rahman, A. F., 77-6589
 Rajalakshmi, S., 77-6254
 Ramioul, L., 77-6569
 Rannie, G. H., 77-6470
 Rao, M. S., 77-6265, 77-6285
 Rappaport, H., 77-6474
 Rasheed, S., 77-6414
 Rastogi, R. B., 77-6247
 Rawls, W. E., 77-6089
 Reddy, B., 77-6388
 Reddy, B. S., 77-6121
 Reddy, C. R., 77-6388
 Reddy, J. K., 77-6265, 77-6285
 Reed, S. I., 77-6420
 Regezi, J. A., 77-6535
 Reich, T., 77-6200
 Reichert, D. F., 77-6100
 Reichert, F., 77-6565
 Reichle, F. A., 77-6457
 Reichle, R. M., 77-6457
 Reitz, M. S., 77-6370
 Reuber, M. D., 77-6134, 77-6252
 Revel, M., 77-6422
 Reynolds, F. H., 77-6315
 Reynolds, R. K., 77-6360
 Reznik, G., 77-6189, 77-6263, 77-6264
 77-6270
 Rhim, J. S., 77-6336, 77-6337, 77-6338
 Rice, J. M., 77-6491
 Richardson, T. G., 77-6289
 Rickart, R., 77-6251
 Rickert, D. E., 77-6015
 Rickinson, A. B., 77-6406
 Rickwood, D., 77-6410
 Riddell, R. H., 77-6504
 Riesenfeld, I., 77-6353
 Rifkin, D., 77-6431
 Rifkin, D. B., 77-6596
 Rinehart, K. L., 77-6359
 Ringold, G. M., 77-6376
 Rinsky, R. A., 77-6145
 Ripper, L. W., 77-6428
 Rivett, K. F., 77-6239
 Robbins, K. C., 77-6343
 Robboy, S. J., 77-6029
 Roberts, R. J., 77-6392, 77-6392
 Robey, W. G., 77-6366
 Robins, R. A., 77-6456
 Robinson, J., 77-6407
 Robinson, S. H., 77-6591
 Roblin, R. O., 77-6464
 Rocchi, P., 77-6293
 Roebuck, B. D., 77-6166
 Rogers, M. J., 77-6427
 Rohrlach, S. T., 77-6596
 Romanenko, V. N., 77-6523
 Romero, C. H., 77-6453, 77-6467
 Rongey, R. W., 77-6414
 Ropcke, G., 77-6235
 Rosenfeld, C., 77-6562
 Rosenkranz, H. S., 77-6306
 Rosenquist, C. J., 77-6149
 Rossi, H. H., 77-6082
 Rossowski, W., 77-6294
 Rovenskii, Iu. A., 77-6598
 Rovera, G., 77-6355
 Rowe, W. P., 77-6350
 Roy, S., 77-6536
 Rozhkova, N. I., 77-6512
 Rubenstein, R., 77-6544
 Ruch, D. G., 77-6336
 Rudali, G., 77-6161, 77-6232

- Ruddick, J. A., 77-6282
 Ruebner, B. H., 77-6513
 Rundell, K., 77-6382
 Rush, M. G., 77-6386
 Russ, G., 77-6325
 Russell, L., 77-6248
 Rutzky, L. P., 77-6503
 Ryan, A. J., 77-6158
 Ryan, D., 77-6202
 Ryzlak, M. T., 77-6457
 Sachdeva, R., 77-6388
 Sachs, L., 77-6553
 Sahgal, S., 77-6532
 Saidel, G., 77-6463
 Sainerova, H., 77-6311
 Sajgo, M., 77-6274
 Sale, G. E., 77-6246
 Sall, S., 77-6524
 Salzman, N. P., 77-6425
 Samuel, E. S., 77-6447
 San, R. H., 77-6287
 Sandberg, A. A., 77-6399
 Sanford, K. K., 77-6597
 Santini, G., 77-6103
 Santos-Ruiz, A., 77-6133
 Sarma, D. S., 77-6254
 Sasaki, M. S., 77-6291
 Sato, J., 77-6516
 Sato, K., 77-6472
 Sauer, G., 77-6419
 Sauron, B., 77-6400
 Savkovic, N., 77-6292
 Saxena, S. C., 77-6239
 Schaller, J. P., 77-6331
 Schara, M., 77-6369
 Scharschmidt, B. F., 77-6507
 Schat, K. A., 77-6328
 Schatt, S., 77-6261
 Schauer, A., 77-6261, 77-6262
 Scherer, E., 77-6250
 Scherer, M. A., 77-6366
 Schidlovsky, G., 77-6413
 Schiffer, D., 77-6002
 Schimpl, A., 77-6484
 Schlauder, M. C., 77-6220
 Schlom, J., 77-6374
 Schmeltz, I., 77-6168, 77-6168, 77-6184
 Schmidbauer, C., 77-6533
 Schmidt-Ullrich, R., 77-6430
 Schreier, H. A., 77-6219
 Schuler, W., 77-6478
 Schumaker, J. A., 77-6071
 Schumann, G., 77-6495
 Schwartz, B. D., 77-6092, 77-6093
 Schwarz, M., 77-6258
 Scordilis, S. P., 77-6421
 Scotto, J., 77-6400
 Scully, P. N., 77-6538
 Scully, R. E., 77-6033
 Segal, A., 77-6240
 Sehgal, C. B., 77-6198, 77-6198
 Seits, I. F., 77-6086
 Selikoff, I. J., 77-6073
 Selkirk, J. K., 77-6212
 Sentjurc, M., 77-6369
 Seth, H. N., 77-6388
 Setlow, R. B., 77-6303
 Seto, A., 77-6496
 Shabad, L. M., 77-6016
 Shain, S. A., 77-6112
 Shani, M., 77-6425
 Shanmugam, G., 77-6362
 Shapiro, P., 77-6513
 Sharma, J. M., 77-6483
 Shaughnessy, E., 77-6219
 Sheahan, D. G., 77-6170
 Shearer, G. M., 77-6450
 Shellenberger, T. E., 77-6229
 Shenk, T., 77-6418
 Sheridan, J. W., 77-6599
 Sherry, N., 77-6219
 Shevach, E. M., 77-6092, 77-6093
 Shevchenko, N. I., 77-6523
 Shigeta, K., 77-6387
 Shimojo, H., 77-6395, 77-6396
 Shiroki, K., 77-6395, 77-6396
 Shiu, R. P., 77-6307
 Shoemaker, E. S., 77-6030
 Shore, S. L., 77-6435, 77-6436
 Shors, E. C., 77-6215
 Shoyab, M., 77-6309, 77-6311
 Shudo, K., 77-6141
 Silverberg, S. G., 77-6541
 Silverman, S., 77-6149
 Silverman, S. J., 77-6297
 Simmon, V. F., 77-6199
 Simpson, M. J., 77-6578
 Singal, D. P., 77-6446
 Singer, B., 77-6006
 Singhal, R. L., 77-6247
 Sinha, D., 77-6203
 Siracka, E., 77-6576
 Siracky, J., 77-6576
 Sirsat, S. M., 77-6144
 Sito, A. F., 77-6324
 Skavronskaia, A. G., 77-6278
 Skeen, P. C., 77-6197
 Slaga, T. J., 77-6079
 Slaney, G., 77-6564
 Slavnaia, I. L., 77-6598
 Small, M., 77-6442
 Smith, A. H., 77-6583
 Smith, C. C., 77-6154
 Smith, G., 77-6188
 Smith, M. E., 77-6470
 Smith, P. G., 77-6079
 Smoler, D., 77-6323
 Smolinsky, S., 77-6560
 Snyder, W. S., 77-6075
 Sobel, M. E., 77-6313
 Soler, M. A., 77-6558
 Solgaard, J., 77-6579
 Solomon, J. J., 77-6240
 Somers, K. D., 77-6368
 Sompayrac, L., 77-6416
 Sonstegard, R. A., 77-6537
 Sorensen, D. K., 77-6332
 Sorenson, G. D., 77-6509
 Souhami, R. L., 77-6556
 Southwick, H. W., 77-6080
 Spahn, G. J., 77-6197
 Speck, W. T., 77-6306
 Spencer, J. L., 77-6482
 Spencer, W. H., 77-6552
 Spiers, A. S., 77-6530
 Spira, M., 77-6518
 Sporn, M. B., 77-6260
 Squire, R. A., 77-6260
 Srai, K. S., 77-6142
 Ssali, J. C., 77-6505
 Stanislas, G., 77-6510
 Stansfeld, A. G., 77-6563
 Stark, G. R., 77-6420
 Steiner, S., 77-6368
 Steinitz, M., 77-6408
 Stekar, J., 77-6284
 Stenback, F., 77-6267
 Stephens, R. E., 77-6594
 Stephenson, J. R., 77-6315, 77-6343
 77-6360
 Stevenet, J., 77-6415
 Stevenson, F. K., 77-6477
 Stevenson, G. T., 77-6477
 Stewart, B. W., 77-6257
 Steyn, P. S., 77-6058
 Stich, H. F., 77-6287, 77-6586
 Stich, W., 77-6287
 Stinson, S. F., 77-6260
 Stockle, G., 77-6251
 Stoffel, P. T., 77-6541
 Stoll, E., 77-6322
 Stone, B. J., 77-6580
 Stone, H. A., 77-6327
 Stoner, G. D., 77-6298
 Strauchen, J. A., 77-6375
 Strauss, B. S., 77-6005
 Streefkerk, D. G., 77-6475
 Strong, L. C., 77-6101
 Suarez, H. G., 77-6415
 Suchomudrenko, A. G., 77-6476
 Sudarsanam, D., 77-6388
 Sugden, B., 77-6405
 Sugino, W. M., 77-6398
 Suk, W. A., 77-6197
 Sullivan, J. P., 77-6275
 Suni, J., 77-6308
 Surjan, A., 77-6274
 Surrey, S., 77-6355
 Sutcliffe, S. B., 77-6563
 Suurkula, M., 77-6451
 Suzuki, H., 77-6499
 Svoboda, J., 77-6308, 77-6311
 Svoboda, V., 77-6301
 Swanson, T. L., 77-6534
 Szyllit, O., 77-6063
 Tabershaw, I. R., 77-6145
 Taguchi, O., 77-6245
 Takasugi, N., 77-6230, 77-6245
 Takayama, S., 77-6526
 Takeda, K., 77-6141
 Takeda, M., 77-6074
 Takemoto, T., 77-6387
 Takenami, T., 77-6387
 Taketa, K., 77-6514
 Talmage, D. W., 77-6443
 Tan, K. B., 77-6423
 Tardiff, R. G., 77-6026, 77-6154
 Tarone, R. E., 77-6597

- Tates, A. D., 77-6281
 Tavitian, A., 77-6348
 Taylor, T. V., 77-6550
 Tegtmeyer, P., 77-6382
 Teplykh, L. A., 77-6299
 Teramoto, Y. A., 77-6374
 Tevethia, M. J., 77-6428, 77-6429
 Tevethia, S. S., 77-6429
 Thakker, D. R., 77-6202, 77-6209
 Thomas, D. B., 77-6116
 Thomas, P. E., 77-6202
 Thompson, D. S., 77-6556
 Thompson, E. I., 77-6563
 Thompson, W. S., 77-6430
 Thomson, A. W., 77-6460
 Thomson, C., 77-6268
 Thor, D. E., 77-6100
 Thorbecke, G. J., 77-6444
 Thust, R., 77-6012
 Tibbetts, C., 77-6393
 Tilson, M. D., 77-6170
 Ting, C. C., 77-6434
 Tipping, E., 77-6142
 Toga, M., 77-6546
 Toivanen, P., 77-6452
 Tom, B. H., 77-6503
 Tomatis, L., 77-6280
 Tomilin, N. V., 77-6130
 Tominaga, T., 77-6573
 Tomita, J. T., 77-6503
 Tong, S., 77-6150
 Topp, W., 77-6431
 Torok, G., 77-6274
 Torrance, B., 77-6550
 Torsuev, N. A., 77-6523
 Toth, B., 77-6168, 77-6168, 77-6172
 Totovic, V., 77-6271
 Towner, J. W., 77-6552
 Toyoshima, K., 77-6317
 Train, R. E., 77-6020
 Trapp, A. L., 77-6015
 Travnicek, M., 77-6319
 Trichopoulos, D., 77-6120
 Troitsky, G. V., 77-6476
 Truhaut, R., 77-6160, 77-6283
 Tsubura, A., 77-6372
 Tsuji, K., 77-6141
 Turler, H., 77-6378
 Turner, D. M., 77-6194
 Turner, J. E., 77-6530
 Turowski, G., 77-6095
 Tutton, P. J., 77-6171, 77-6566
 Tuyns, A. J., 77-6569
 Tyroler, H. A., 77-6583
 Ueda, M., 77-6514
 Ushimaru, Y., 77-6173, 77-6177
 Vadi, H., 77-6204
 Vaheri, A., 77-6308
 Vakil, D. V., 77-6574
 Valerio, M. G., 77-6508
 Valladares, Y., 77-6085
 Van Emmelo, J., 77-6320
 Van Ert, M., 77-6583
 Van Miller, J. P., 77-6156
 Vana, J., 77-6237
 Vande Woude, G. F., 77-6366
 Vanderlaan, M., 77-6305
 Varmus, H. E., 77-6376
 Vasil'eva, S. V., 77-6278
 Venuat, A. M., 77-6562
 Verma, S. P., 77-6430
 Vernon, M. L., 77-6336
 Vestergaard, B. F., 77-6401
 Vigne, R., 77-6333
 Vogt, P. K., 77-6330
 Voll, M. J., 77-6296
 Vuataz, L., 77-6290
 Wachtel, E., 77-6384
 Waghlikar, U. L., 77-6388
 Wagoner, J. K., 77-6145
 Walker, D. A., 77-6539
 Wallach, D. F., 77-6430
 Wallcave, L., 77-6168, 77-6168
 Walters, C. L., 77-6266
 Wanebo, H. J., 77-6454
 Wang, D. Y., 77-6531
 Wang, S. Y., 77-6316
 Warnatz, H., 77-6099
 Warr, G. A., 77-6192, 77-6193
 Watanabe, A., 77-6514
 Waters, E. M., 77-6050
 Waye, J. D., 77-6109
 Weberg, A. D., 77-6368
 Wecker, E., 77-6484
 Wedderburn, N., 77-6458
 Weiler, E., 77-6478
 Weill-Thevenet, N., 77-6225
 Weinberg, J. B., 77-6462
 Weinhold, K. J., 77-6455
 Weisburger, E. K., 77-6295
 Weisburger, J. H., 77-6064
 Weiss, S. B., 77-6208
 Weiss, W., 77-6071
 Weissman, S. M., 77-6417
 Weissmann, C., 77-6322
 Welch, W. R., 77-6029
 Wellings, S. R., 77-6587
 Wheeler, E., 77-6445
 Wheelock, E. F., 77-6356, 77-6455
 Whitehouse, J. M., 77-6563
 Whitmire, C. E., 77-6196
 Whittle, K. J., 77-6025
 Wigzell, H., 77-6450
 Williams, C. J., 77-6373
 Williams, D. C., 77-6182
 Williams, E. D., 77-6539, 77-6540
 Williams, W. L., 77-6175
 Williamson, D., 77-6162
 Wilson, J. H., 77-6433
 Wilson, M. G., 77-6552
 Wilton, L. V., 77-6190
 Winkelstein, W., 77-6072
 Winkler, G., 77-6238
 Winocour, E., 77-6422
 Winston, V. D., 77-6381
 Wishnok, J. S., 77-6065
 Witschi, H., 77-6162
 Wolfgang, P. E., 77-6031
 Wong, J. L., 77-6275
 Wong, P. K., 77-6361
 Wood, A. W., 77-6202, 77-6209
 Woodhead, A. D., 77-6538
 Woodruff, R. K., 77-6563
 Woolnough, J. A., 77-6443
 Workshop on Lung Cancer, 77-6127
 Worley, M. B., 77-6440
 Wozniak, K. J., 77-6535
 Wright, M. J., 77-6567
 Wright, P. J., 77-6382
 Wu, A. M., 77-6370
 Wurzner, H. P., 77-6290
 Wynder, E. L., 77-6233
 Yager, J. D., 77-6167
 Yagi, H., 77-6202, 77-6209
 Yakobson, E., 77-6422
 Yakovleva, L. S., 77-6329
 Yamada, K. M., 77-6313
 Yamashiro, K., 77-6499
 Yamazaki, F., 77-6586
 Yanagi, K., 77-6386
 Yanai, R., 77-6372
 Yang, J. P., 77-6557
 Yano, S., 77-6395
 Yasui, T., 77-6230
 Yee, C., 77-6383
 Yevich, P. P., 77-6568
 Yogore, M. G., 77-6532
 Yokoyama, M., 77-6515
 Yoshida, A., 77-6277
 Yoshida, M., 77-6317
 Yoshinaka, Y., 77-6358
 Young, J. M., 77-6374
 Young, N. A., 77-6375
 Young, R. J., 77-6145
 Yuen, P. H., 77-6361
 Zack, M. M., 77-6570
 Zamecnik, P. C., 77-6488
 Zapol'skaia, N. A., 77-6299
 Zargi, M., 77-6243
 Zav'yalov, V. P., 77-6476
 Zhdanov, V. M., 77-6326
 Zimmerman, D. E., 77-6541

Subject Index

Abnormalities

- Estradiol
 - Vagina, Mouse, 77-6230
- Retinol Acetate
 - Vagina, Mouse, 77-6230

Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-

- Carbamic Acid, Diethyldithio-
 - DNA, Liver, 77-6254
- Chromosome Aberrations
 - Xeroderma Pigmentosum, 77-6287
- DNA Repair
 - Cells, Cultured, 77-6005, 77-6303
 - Xeroderma Pigmentosum, 77-6287

Acetamide, *N*-Fluoren-2-yl-

- Cytochrome P-450
 - Metabolism, 77-6018
- Hepatoma
 - Mouse, 77-6135
 - Transplacental Carcinogenesis, 77-6135
- Liver
 - Ultrastructural Study, Rat, 77-6136
- Liver Neoplasms
 - Histological Study, Mouse, 77-6241
 - Phorbol, 77-6135
- Sarcoma, Reticulum Cell
 - Mouse, 77-6135

Acetamide, Thio-

- Ligases
 - Mitochondria, 77-6133
- Liver
 - Mitochondria, 77-6133
- Ornithine Carbamoyltransferase
 - Mitochondria, 77-6133
- RNA Polymerase
 - Chromatin, Binding, 77-6132
 - Liver, Rat, 77-6132

Acetanilide, 4'-(*p*-Fluorophenyl)-

- Mammary Neoplasms, Experimental
 - Carcinoma, 77-6134
 - Nephrectomy, 77-6134

Acetanilide, 4'-Hydroxy-

- Cytochrome P-450
 - Metabolism, 77-6018

Acetic Acid, (*N*-Acetyl-*N*-2-phenanthryl)amino) Ester

- DNA
 - Acetylation and Phenanthrylation, 77-6137
 - Modification, Structural, 77-6137

Acetic Acid, 2,4-Dichlorophenoxy-

- Carcinogenic Potential
 - Mouse, 77-6052
 - Rat, 77-6052
- Hemangioma
 - Rat, 77-6052

Acetic Acid, 2,4-Dichlorophenoxy- (cont'd)

- Mammary Neoplasms, Experimental
 - Adenofibroma, 77-6052
- Sarcoma, Reticulum Cell
 - Mouse, 77-6052

Acetic Acid, Ester with 2,6-Dimethyl-*m*-dioxan-4-ol

- Fibrosarcoma
 - Rat, 77-6048
- Head and Neck Neoplasms
 - Carcinoma, Epidermoid, 77-6048
- Hepatoma
 - Rat, 77-6048
- Kidney Neoplasms
 - Carcinoma, Transitional Cell, 77-6048
- Leukemia
 - Rat, 77-6048
- Liver Neoplasms
 - Rat, 77-6048
- Lymphosarcoma
 - Rat, 77-6048

Acetic Acid, (Ethylenebis(oxyethylenitrilo))tetra-

- Virus, Polyoma
 - Viral Proteins, 77-6381

Acetic Acid, 2,4,5-Trichlorophenoxy-

- Carcinogenic Potential
 - Mouse, 77-6051
- Hepatoma
 - Mouse, 77-6051
- Mouse
 - Carcinogenic Potential, 77-6161

Acetohydroxamic Acid, *N*-Fluoren-2-yl-

- Carbamic Acid, Diethyldithio-
 - DNA, Liver, 77-6254

N-Acetoxy-*N*-2-acetylaminophenanthrene

- see Acetic Acid, (*N*-Acetyl-*N*-2-phenanthryl)amino) Ester

Acrolein

- Carcinogenic Potential
 - Hamster, 77-6214
- Respiratory Tract Neoplasms
 - Hamster, 77-6214

Adenine, 1-(2-Carboxyethyl)-

- 2-Oxetanone
 - DNA, 77-6240
 - Isolation and Characterization, 77-6240

Adenocarcinoma

- Bladder Neoplasms
 - 1-Butanol, 4-(Butylnitrosamino)-, 77-6262
- Breast Neoplasms
 - Epidemiology, 77-6574
- Carrageen
 - Dose-Response Study, Mouse, 77-6460
 - Transplantation Immunology, 77-6460
- Colonic Neoplasms
 - Cell Division, 77-6171
 - Hydrazine, 1,1-Dimethyl-, 77-6171
 - Naphthalene, 1-Nitroso-, 77-6286
 - Transplantation, Heterologous, 77-6503

Adenocarcinoma (cont'd)

- Digestive System Neoplasms
 - Carcinogenic Potential, Hamster, 77-6248
- Gynecologic Neoplasms
 - Estradiol, 77-6229
 - 4,4'-Stilbenediol, α,α' -Diethyl-, 77-6229
- Intestinal Neoplasms
 - Neoplasms, Multiple Primary, 77-6550
- Kidney Neoplasms
 - Virus, Lucke Herpes, 77-6567
- Lung Neoplasms
 - Arsenic, 77-6222
 - Arsenic Trioxide, 77-6222
 - p*-Benzoquinone, 77-6049
 - Succinic Acid, Mono(2,2-dimethylhydrazide) 77-6168
- Mammary Neoplasms, Experimental
 - Precancerous Conditions, 77-6229
 - Virus, Murine Mammary Tumor, 77-6372
- Nose Neoplasms
 - Epidemiology, 77-6113, 77-6579
- Prostatic Neoplasms
 - Histological Study, 77-6112
 - Rat, 77-6112
- Respiratory Tract Neoplasms
 - Ethenamine, *N*-Ethylene-*N*-nitroso-, 77-6248
 - 2-Propanol, 1,1'-Iminodi-*N*-nitroso-, 77-6263
- Thyroid Neoplasms
 - Neoplasms, Multiple Primary, 77-6543
- Vaginal Neoplasms
 - 4,4'-Stilbenediol, α,α' -Diethyl-, 77-6113

Adenofibroma

- Mammary Neoplasms, Experimental
 - Acetic Acid, 2,4-Dichlorophenoxy-, 77-6052
 - Caffeine, 77-6290
 - Fluorescein, 2',4',5',7'-Tetrabromo-, Disodium Salt 77-6055

Adenoma

- Adrenal Gland Neoplasms
 - Caffeine, 77-6290
- Kidney Neoplasms
 - Dimethylamine, *N*-Nitroso-, 77-6255
 - Succinic Acid, Mono(2,2-dimethylhydrazide) 77-6168
- Liver Neoplasms
 - Androsta-1,4-dien-3-one, 17-Hydroxy-17-methyl- 77-6244
 - Contraceptives, Oral, 77-6036, 77-6237
 - Epidemiology, 77-6237
- Lung Neoplasms
 - Arsenic, 77-6222
 - Arsenic Trioxide, 77-6222
 - Carbamic Acid, Ethyl Ester, 77-6162, 77-6163
 - Cell-cycle Kinetics, 77-6163
 - Guanidine, Dodecyl-, Acetate, 77-6274
 - Guanidine, Methyl-, 77-6274
 - Naphthalene, 2-Nitroso-, 77-6286
 - Resorcinol, 77-6042
 - Smoking, 77-6189
 - Succinic Acid, Mono(2,2-dimethylhydrazide) 77-6168
 - Urea, Ethyl Nitroso-, 77-6280
- Mammary Neoplasms, Experimental
 - DU 41274, 77-6239
- Pancreatic Neoplasms
 - Propanol, 1,1'-Iminodi-*N*-nitroso-, 77-6265

Adenoma (cont'd)

- Stomach Neoplasms
 - Histological Study, 77-6500
- Thyroid Neoplasms
 - Isopropyl Oils, 77-6054
- Adenoma, Chromophobe**
 - Pituitary Neoplasms
 - Ultrastructural Study, 77-6536
- Adenosine Cyclic 3',5' Monophosphate**
 - Proteins
 - Degradation, Intracellular, 77-6588
 - Virus, Avian Sarcoma
 - Cell Transformation, Neoplastic, 77-6317
 - Virus, Murine Sarcoma
 - Cell Transformation, Neoplastic, 77-6368
- Adenyl Cyclase**
 - Virus, Avian Sarcoma
 - Cell Transformation, Neoplastic, 77-6317
- Adrenal Gland Neoplasms**
 - Adenoma
 - Caffeine, 77-6290
 - Caffeine
 - Dose-Response Study, Rat, 77-6290
 - Methane, Dichloro-, 77-6290
- Aflatoxin B1**
 - Carbamic Acid, Diethyldithio-
 - DNA, Liver, 77-6254
 - Cells, Cultured
 - Metabolism, 77-6298
 - Corticotropin
 - Carcinogenic Activity, Rat, 77-6174
 - Hepatoma
 - Corticotropin, 77-6174
 - Insulin, 77-6174
 - Somatotropin, 77-6174
 - Liver
 - Metabolism, 77-6058
 - Lymphoma
 - Corticotropin, 77-6174
 - Toxicology
 - Dog, 77-6175
- Agammaglobulinemia**
 - Virus, Herpes Simplex
 - Killer Cells, 77-6435
- Agglutination**
 - Smoking
 - Macrophages, 77-6192
 - Virus, Murine Sarcoma
 - Cell Transformation, Neoplastic, 77-6368
- Aging**
 - Cell Transformation, Neoplastic
 - Cell Cycle Kinetics, Review, 77-6128
 - T-Lymphocytes
 - Immune Response, 77-6097
- Agrobacterium tumefaciens**
 - DNA, Bacterial
 - Isolation and Characterization, 77-6131
 - Plant Tumors
 - DNA, Bacterial, 77-6131
- Air Pollutants**
 - Benzo(a)pyrene
 - Automobile Exhaust, 77-6016

- Air Pollutants (cont'd)**
 Mutagenic Activity, 77-6199
Salmonella typhimurium
 Mutagenic Activity, 77-6199
- Air Pollution**
 Lung Neoplasms
 Epidemiology, Review, 77-6127
- Alanine, 3-(p-(Bis(2-chloroethyl)amino)phenyl)-**
 Antineoplastic Agents
 Purine-6-thiol, 77-6295
- Alanine, 3-(3,4-Dihydroxyphenyl)-**
 Melanoma
 Review, 77-6060
- Alcohol Drinking**
 Mouth Neoplasms
 Diagnosis and Prognosis, 77-6183
- Alginic Acid, Sodium Salt**
 Cesium Radioisotopes
 Cell Transformation, Neoplastic, 77-6299
 Strontium Radioisotopes
 Cell Transformation, Neoplastic, 77-6299
- Alkaline Phosphatase**
 Sarcoma, Osteogenic
 Virus, Moloney Murine Sarcoma, 77-6365
- Americium**
 Plutonium
 Dose-Response Study, 77-6075
- o-Aminodiphenyl**
 see 2-Biphenylamine
- Amyloidosis**
 Thyroid Neoplasms
 Carcinoma, 77-6542
- Androgens**
 Hepatoma
 Histological Study, 77-6246
 Kidney Neoplasms
 Case Report, 77-6246
 Histological Study, 77-6246
 Metabolism
 Review, 77-6037
 Pancreatic Neoplasms
 Case Report, 77-6246
 Hepatoma, 77-6246
 Histological Study, 77-6246
- Androsta-1,4-dien-3-one, 17-Hydroxy-17-methyl-**
 Hepatoma
 Neoplasms, Multiple Primary, 77-6244
 Liver Neoplasms
 Adenoma, 77-6244
 Case Report, 77-6244
 Neoplasms, Multiple Primary, 77-6244
- Anemia, Aplastic**
 Liver Neoplasms
 Case Report, 77-6513
- Angioma**
 see Hemangioma
- Angiosarcoma**
 Liver Neoplasms
- Angiosarcoma (cont'd)**
 Ethylene, Chloro-, 77-6113
 Propanol, 1,1'-Iminodi-N-nitroso-, 77-6265
 Urea, Methyl Nitroso-, 77-6277
 Succinic Acid, Mono(2,2-dimethylhydrazide)
 Mouse, 77-6168
- Aniline, N,N-Dimethyl-p-phenylazo-**
 Hepatoma
 Radiation, Ionizing, 77-6456
- Anisole, p-Allyl-**
Salmonella typhimurium
 Mutagenic Activity, 77-6146
- 2-Anthracenamide**
 5 β -Cholan-24-oic Acid, 3 α -Hydroxy-
 Mutagenic Activity, 77-6297
Salmonella typhimurium
 Mutagenic Activity, 77-6198
- Anthracene**
 Lipids
 Cell Membrane, 77-6210
 Neoplasms
 Epidemiology, 77-6200
- Anthraquinone**
 Mutagenic Activity
 Purine-6-thiol, 77-6179
Salmonella typhimurium, 77-6179
- Anti-Antibodies**
 Lymphoid Tissue
 Rosette Formation, Chick, 77-6472
- Antibodies, Viral**
 Bladder Neoplasms
 Virus, Papova, 77-6383
 Burkitt's Lymphoma
 Virus, Epstein-Barr, 77-6438
 Nasopharyngeal Neoplasms
 Carcinoma, 77-6404
 Virus, Epstein-Barr, 77-6404
 Neoplasms
 Virus, Papova, 77-6383
 Virus, Feline Leukemia
 Cats, 77-6440
 Virus, Herpes Simplex 2
 Antigen-Antibody Reactions, 77-6401
 Immunosorbent Assay, 77-6401
 Virus, Polyoma BK
 Pregnancy, 77-6385
 Virus, Polyoma JC
 Pregnancy, 77-6385
- Antibody Formation**
 Carcinogen, Chemical
 Immunosuppression, Review, 77-6100
 Cholanthrene, 3-Methyl-
 Strain Difference, Mouse, 77-6196
 Graft vs Host Reaction
 Immunosuppression, 77-6449
 B-Lymphocytes
 Chick Embryo, 77-6452
 Virus, Adeno 3
 Age Factors, 77-6334
 Virus, Avian Leukosis
 Histocompatibility Antigens, 77-6467

Antibody Formation (cont'd)

- B-Lymphocytes, 77-6467
- Virus, Herpes Simplex 1
 - Effector Cell, 77-6486
 - Gamma Globulins, 77-6486
 - IgG, 77-6486
 - Immunoglobulins, Fc, 77-6486
- Virus, Rous Sarcoma
 - Estr-4-en-3-one, 7 α ,17-Dimethyl-17 β -Hydroxy 77-6453

Antibody Specificity

- Melanoma
 - Carcinoembryonic Antigen, 77-6485

Antigen-Antibody Reactions

- Kidney Neoplasms
 - Virus, Lucke Herpes, 77-6567
- Nasopharyngeal Neoplasms
 - Virus, Epstein-Barr, 77-6403
- Neoplasms, Experimental
 - Virus, Adeno 7 - SV40 Hybrid, 77-6439
- Virus, Adeno 7 - SV40 Hybrid
 - Complement, 77-6439
 - Immunity, Cellular, 77-6439
- Virus, C-Type RNA Tumor
 - Immune Serums, 77-6495
 - Immunosuppression, 77-6495
- Virus, Friend Murine Leukemia
 - Viral Proteins, 77-6484
- Virus, Herpes Simplex 1
 - Immunity, Cellular, 77-6486
- Virus, Herpes Simplex 2
 - Antibodies, Viral, 77-6401
- Virus, SV40
 - Antigens, Viral, 77-6426

Antigenic Determinants

- Cholanthrene, 3-Methyl-
 - Cell Transformation, Neoplastic, 77-6481
- Plasmacytoma
 - Cell Membrane, 77-6479
 - Myeloma Proteins, 77-6479
- Sarcoma
 - Antigens, Neoplasm, 77-6493
 - Cholanthrene, 3-Methyl-, 77-6493
 - Transplantation Immunology, 77-6493
- Virus, Adeno
 - Mouse FL Strain, 77-6335
- Virus, Avian Leukosis
 - Cell Transformation, Neoplastic, 77-6481
 - Immunity, Cellular, 77-6481
 - Virus Replication, 77-6481
- Virus, Avian Sarcoma
 - Cell Transformation, Neoplastic, 77-6481
 - Immunity, Cellular, 77-6481
 - Virus Replication, 77-6481
- Virus, Herpes
 - Guinea Pig, 77-6338
- Virus, SV40
 - Antigens, Viral, 77-6426

Antigens

- Hodgkin's Disease
 - Cells, Cultured, 77-6488
 - Isolation and Characterization, 77-6488
- Leukemia, Lymphoblastic
 - B-Lymphocytes, 77-6103
 - T-Lymphocytes, 77-6103

Antigens (cont'd)

- Leukemia, Lymphocytic
 - B-Lymphocytes, 77-6103
 - T-Lymphocytes, 77-6103

Antigens, Heterogenetic

- Fibrosarcoma
 - Hypersensitivity, Delayed, 77-6444

Antigens, Neoplasm

- Cholangioma
 - Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-, 77-6494
- Hepatoma
 - Transplantation Immunology, 77-6456
- Hodgkin's Disease
 - Isolation and Characterization, 77-6489
- Leukemia
 - Guinea Pig, 77-6092
- Liver Neoplasms
 - Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-, 77-6494
- Lung Neoplasms
 - Transplacental Carcinogenesis, 77-6491
- T-Lymphocytes
 - Immune Response, 77-6441
 - Immunity, Cellular, 77-6486
 - Migration Inhibitory Factor, 77-6486
- Neoplasms, Experimental
 - Cholanthrene, 3-Methyl-, 77-6099
- Plasmacytoma
 - IgA, 77-6479
- Respiratory Tract Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-6492
 - Benzo(a)pyrene, 77-6492
 - Carcinoma, Epidermoid, 77-6492
 - Cholanthrene, 3-Methyl-, 77-6492
- Sarcoma
 - Antigenic Determinants, 77-6493
 - Cholanthrene, 3-Methyl-, 77-6490
 - Isolation and Characterization, 77-6490
- Virus, Marek's Disease Herpes
 - Viral Vaccines, 77-6483
- Virus, Turkey Herpes, 77-6483
- Virus, SV40
 - Immune Response, 77-6441

Antigens, Viral

- Burkitt's Lymphoma
 - Virus, Epstein-Barr, 77-6409, 77-6412
- Chromatin
 - Isolation and Characterization, 77-6410
- Erythroleukemia
 - Virus, Friend Murine Leukemia, 77-6356
- Infectious Mononucleosis
 - Virus, Epstein-Barr, 77-6409
- Interferon
 - Virus, Murine Mammary Tumor, 77-6375
- Uridine, 2'-Deoxy-5-iodo-
 - Organ Culture, 77-6353
- Virus, Adeno-Associated
 - Virus Replication, 77-6396
- Virus, Avian Myeloblastosis
 - Isolation and Characterization, 77-6325
 - Reverse Transcriptase, 77-6324
 - Viral Proteins, 77-6324
- Virus, Avian Sarcoma
 - Isolation and Characterization, 77-6312
- Virus, Bovine Leukemia

- Antigens, Viral (cont'd)**
 - Lymphocytes, 77-6087
 - Virus, C-Type RNA Tumor
 - Cells, Cultured, 77-6349
 - Virus, Epstein-Barr
 - Baboon, 77-6413
 - Binding, Iodinated Antibodies, 77-6409
 - Burkitt's Lymphoma, 77-6438
 - Chimpanzee, 77-6413
 - Isolation and Characterization, 77-6410, 77-6411
 - Quantitation Method, 77-6409
 - Virus, Feline Leukemia
 - Horizontal Transmission, 77-6331
 - Leukocytes, 77-6331
 - Virus, Gross Murine Leukemia
 - Mouse, 77-6351
 - Virus, Herpes Simplex 1
 - Cells, Cultured, 77-6397
 - Virus, Herpes Simplex 2
 - Cells, Cultured, 77-6397
 - Virus, Lucke Herpes
 - Ultrastructural Study, Ascites Cells, 77-6567
 - Virus, Murine Leukemia
 - Organ Culture, 77-6353
 - Precancerous Conditions, 77-6352
 - Thymus Gland, 77-6352
 - Virus, SV40
 - Antigen-Antibody Reactions, 77-6426
 - Antigenic Determinants, 77-6426
 - Carcinoembryonic Antigen, 77-6426
 - Cell Membrane, 77-6427
 - Cell Transformation, Neoplastic, 77-6426
 - DNA Replication, 77-6419
 - Temperature Sensitive Mutants, 77-6428, 77-6429
- Antilymphocyte Serum**
 - T-Lymphocytes
 - Rosette Formation, Chick, 77-6472
 - Virus, Adeno 3
 - Immune Response, 77-6334
 - T-Lymphocytes, 77-6334
- Antimony Oxide**
 - Toxicology
 - Review, 77-6151
- Antineoplastic Agents**
 - Alanine, 3-(*p*-(Bis(2-chloroethyl)amino)phenyl)-
 - Purine-6-thiol, 77-6295
 - Imidazole-4-carboxamide, 5-(3,3-Dimethyl-1-triazeno)-
 - Carcinogenic Activity, Mouse, 77-6295
 - Purine-6-thiol
 - Carcinogenic Activity, Mouse, 77-6295
 - Streptozotocin
 - Purine-6-thiol, 77-6295
 - p*-Toluamide, *N*-Isopropyl- α -(2-methylhydrazino)-, HCl
 - Carcinogenic Activity, Mouse, 77-6295
- Antipyrine**
 - Liver
 - Metabolism, 77-6180
- Aramite**
 - Diet
 - Metabolism, Rat, 77-6160
 - 2-Propanol, 1-(*p*-*t*-Butylphenoxy)-
 - Carcinogenic Metabolite, 77-6160
- Arsenic**
 - Benzo(a)pyrene
- Arsenic (cont'd)**
 - Co-carcinogenic Activity, 77-6222
 - Carcinogen, Environmental
 - Toxicity, Review, 77-6014
 - Gastrointestinal System
 - Toxicity, Review, 77-6014
 - Leukemia
 - Toxicity, Review, 77-6014
 - Lung Neoplasms
 - Adenocarcinoma, 77-6222
 - Adenoma, 77-6222
 - Epidemiology, 77-6223
- Arsenic Trioxide**
 - Benzo(a)pyrene
 - Co-carcinogenic Activity, 77-6222
 - Lung Neoplasms
 - Adenocarcinoma, 77-6222
 - Adenoma, 77-6222
 - Benzo(a)pyrene, 77-6222
- Aryl Hydrocarbon Hydroxylases**
 - Barbituric Acid, 5-Ethyl-5-phenyl-
 - Enzymatic Activity, 77-6198
 - Benzo(a)pyrene
 - Colon, 77-6212
 - Liver, Mouse, 77-6216
 - Retinol Acetate, 77-6212
 - Trace Elements, 77-6216
 - Cholanthrene, 3-Methyl-
 - Enzymatic Activity, 77-6198
 - Enzymatic Activity, Hamster, Rat, 77-6194
 - Ethyl Alcohol
 - DNA, 77-6182
 - Polychlorobiphenyl Compounds
 - Enzymatic Activity, 77-6198
 - Smoking
 - Enzymatic Activity, Hamster, Rat, 77-6194
 - Lymphocytes, 77-6193
 - Macrophages, 77-6192, 77-6193
 - Tars
 - Lymphocytes, 77-6193
 - Macrophages, 77-6193
- Asbestos**
 - Bronchial Neoplasms
 - Carcinoma, 77-6577, 77-6578
 - Epidemiology, 77-6577, 77-6578
 - Mesothelioma, 77-6578
 - Gastrointestinal Neoplasms
 - Carcinoma, 77-6073
 - Laryngeal Neoplasms
 - Carcinoma, 77-6073
 - Lung Neoplasms
 - Carcinoma, 77-6073
 - Case Report, 77-6074
 - Epidemiology, 77-6074, 77-6577, 77-6578
 - Mesothelioma, 77-6577, 77-6578
 - Macrophages
 - Immune Response, 77-6465
 - Neoplasms
 - Review, 77-6073
 - Peritoneal Neoplasms
 - Mesothelioma, 77-6073, 77-6113
 - Pleural Neoplasms
 - Mesothelioma, 77-6073, 77-6113
 - Water Pollution
 - Legal Aspects, Review, 77-6021

- Ascorbic Acid**
 4-Biphenylamine
 Metabolism, Dog, 77-6147
 Nitrosamines
 Stomach Neoplasms, 77-6064
- Aspergillus parasiticus***
 Lymphocytes
 Chromosome Abnormalities, 77-6176
 Mitosis, 77-6176
 Mycotoxins
 Chromosome Abnormalities, 77-6176
- Aspergillus tamarii***
 Lymphocytes
 Mitosis, 77-6176
- Astrocytoma**
 Brain Neoplasms
 Lead, 77-6219
- Australia Antigen**
 Hepatoma
 Antigen Frequency, 77-6388
 Liver Cirrhosis, 77-6388
 Liver Neoplasms
 Epidemiology, 77-6387
- Autoimmune Diseases**
 Histocompatibility Antigens
 Immune Response, Review, 77-6096
- Automobile Exhaust**
 Benzo(a)pyrene
 Air Pollutants, 77-6016
 Carcinogenic Potential, Review, 77-6016
 Polycyclic Hydrocarbons
 Carcinogenic Potential, Review, 77-6016
- Azathioprine**
 Bronchial Neoplasms
 Benzo(a)pyrene, 77-6215
 Urea, Methyl Nitroso-, 77-6215
- Azo Compounds**
 Carrier Proteins
 Metabolism, Liver, 77-6142
- Bacillus megaterium***
 Immunity, Cellular, 77-6459
- Bacteria**
 Benzoic Acid, *p*-Hydroxy-
 Degradation, Review, 77-6062
 Pesticides
 Degradation, Review, 77-6062
 Polycyclic Hydrocarbons
 Degradation, Review, 77-6062
- Bacteriophages**
 RNA, Viral
 Poly A, 77-6320
 Reverse Transcriptase
 RNA Replication, 77-6320
- Barbituric Acid, 5-(1-Cyclohexen-1-yl)-1,5-dimethyl-**
 Liver
 Metabolism, 77-6180
- Barbituric Acid, 5-Ethyl-5-phenyl-**
 Aryl Hydrocarbon Hydroxylases
 Enzymatic Activity, 77-6198
 Benzo(a)pyrene
 Metabolism, Colon, 77-6212
- Barbituric Acid, 5-Ethyl-5-phenyl- (cont'd)**
 Dimethylamine, *N*-Nitroso-
 1-Propanone, 2-Methyl-1,2-di-3-pyridyl-, Tartrate
 77-6258
 Liver Neoplasms
 Diethylamine, *N*-Nitroso-, 77-6004
 Oxidoreductases
 Review, 77-6009
- BCG**
 Carrageen
 Immunity, Cellular, 77-6461
 Fibrosarcoma
 Benz(a)anthracene, 7,12-Dimethyl-, 77-6461
 Immunity, Cellular, 77-6461
 T-Lymphocytes
 Transplantation Immunology, 77-6445
 Sarcoma
 Benzo(a)pyrene, 77-6445
 T-Lymphocytes, 77-6445
 Transplantation Immunology, 77-6445
 Silica, Crystalline
 Immunity, Cellular, 77-6461
- Bence Jones Protein**
 Multiple Myeloma
 Temperature Dependence, 77-6476
- Bencyclane**
 Neoplasm Metastasis
 Platelet Aggregation, 77-6549
- Benz(a)anthracene**
 Benzo(a)pyrene
 Colon, 77-6212
- Benz(a)anthracene, 7,12-Dimethyl-**
 Fibrosarcoma
 BCG, 77-6461
Corynebacterium parvum, 77-6461
 Transplantation Immunology, 77-6444
 Mammary Neoplasms, Experimental
 Histological Study, 77-6529
 Precancerous Conditions, 77-6203
 Tissue Extracts, Liver, Fetus, 77-6457
 Neoplasms, Experimental
 Transplantation Immunology, 77-6447
 Respiratory Tract Neoplasms
 Antigens, Neoplasm, 77-6492
Salmonella typhimurium
 Mutagenic Activity, 77-6198
 Skin Neoplasms
 Carcinogenic Activity, Review, 77-6010
 12-*O*-Tetradecanoylphorbol-13-acetate
 77-6010
 Ultraviolet Rays
 Co-carcinogenic Activity, Review, 77-6010
- Benz(a)anthracene, 12-Methyl-**
 Carcinogenic Potential
 Models, Theoretical, 77-6201
- Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-**
 Cholangioma
 Antigens, Neoplasm, 77-6494
 Liver
 Ultrastructural Study, Rat, 77-6136
 Liver Neoplasms
 Antigens, Neoplasm, 77-6494

Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)- (cont'd)
Carcinoma, 77-6494

Benzene

- Leukemia
 - Epidemiology, Review, 77-6104
- Leukemia, Monoblastic
 - Occupational Hazard, 77-6145
- Leukemia, Myeloblastic
 - Occupational Hazard, 77-6145
- Radiation, Ionizing
 - Epidemiology, 77-6125
- Skin
 - Ultrastructural Study, Mouse, 77-6144

**Benzene, 4-Allyl-1,2-(methylenedioxy)-
Biphenyl**

- Metabolism, 77-6150
- 2-Biphenylol
 - Fluorimetric Assay, 77-6150
- 4-Biphenylol
 - Fluorimetric Assay, 77-6150
- Microsomes, Liver
 - Metabolism, 77-6150
- Salmonella typhimurium*
 - Mutagenic Activity, 77-6146

Benzene, 1,4-Bis(chloromethoxymethyl)-

- Carcinoma, Epidermoid
 - Mouse, 77-6043
- Sarcoma
 - Mouse, 77-6043
- Skin Neoplasms
 - Papilloma, 77-6043

Benzene, (Epoxyethyl)-

- Epoxide Hydratases
 - Metabolism, 77-6158
- Transferases
 - Metabolism, 77-6158

1,2-Benzisothiazolin-3-one, 1,1-Dioxide

- Bladder Neoplasms
 - Epidemiology, 77-6059

Benzo(a)pyrene

- Air Pollutants
 - Automobile Exhaust, 77-6016
 - Mutagenic Activity, 77-6199
- Arsenic
 - Co-carcinogenic Activity, 77-6222
- Arsenic Trioxide
 - Co-carcinogenic Activity, 77-6222
- Aryl Hydrocarbon Hydroxylases
 - Liver, Mouse, 77-6216
 - Trace Elements, 77-6216
- Automobile Exhaust
 - Carcinogenic Potential, Review, 77-6016
- Barbituric acid, 5-Ethyl-5-phenyl-
 - Metabolism, Colon, 77-6212
- Benz(a)anthracene
 - Colon, 77-6212
- 7,8-Benzoflavone
 - Colon, 77-6212
 - DNA, Binding, 77-6204
 - Metabolism, Rat, 77-6204
- Bronchial Neoplasms
 - Animal Model, Dog, 77-6215
 - Azathioprine, 77-6215
 - Precancerous Conditions, 77-6215

Benzo(a)pyrene (cont'd)

- Prednisolone, Methyl-, 77-6215
- Carcinogenic Potential
 - Models, Theoretical, 77-6201
- Cell Transformation, Neoplastic
 - Dose-Response Study, 77-6013
 - Fluorescamine Labeling, 77-6340
- Cells, Cultured
 - Metabolism, 77-6298
 - Mutagenic Activity, Diol Epoxides, 77-6209
- Colon
 - Aryl Hydrocarbon Hydroxylases, 77-6212
 - Carcinogenic Metabolite, 77-6212
 - DNA, Binding, 77-6212
- Cyclohexane, 1,2,3,4,5,6-Hexachloro-, γ -Isomer
 - Carcinogenic Metabolite, 77-6205
- Cytochrome P-450
 - Metabolism, 77-6018
- Disulfide, Bis(diethylthiocarbamoyl)-
 - Colon, 77-6212
- DNA
 - Enzymatic Activity, 77-6182
- Ethyl Alcohol
 - Metabolism, 77-6182
- Lipids
 - Cell Membrane, 77-6210
- Liver
 - DNA, Binding, 77-6204
 - Metabolism, 77-6180
 - Metabolism, Rat, 77-6204
- Lung Neoplasms
 - Arsenic Trioxide, 77-6222
 - Carcinoma, Epidermoid, 77-6222
 - Coal, 77-6582
- Maleic Acid, Diethyl Ester
 - DNA, Binding, 77-6204
 - Metabolism, Rat, 77-6204
- Mammary Neoplasms, Experimental
 - Histological Study, 77-6528
- Propane, 1,2-Epoxy-3,3,3-trichloro-
 - DNA, Binding, 77-6204
 - Hydro-Lyases, 77-6213
 - Metabolism, Rat, 77-6204
- Respiratory Tract Neoplasms
 - Antigens, Neoplasm, 77-6492
 - Dose-Response Study, Hamster, 77-6211
 - Hamster, 77-6214
 - Solvents, 77-6211
- Retinol Acetate
 - Aryl Hydrocarbon Hydroxylases, 77-6212
- Salicylamide
 - DNA, Binding, 77-6204
 - Metabolism, Rat, 77-6204
- Salmonella typhimurium*
 - Mutagenic Activity, 77-6061, 77-6198
 - Mutagenic Activity, Diol Epoxides, 77-6209
- Sarcoma
 - BCG, 77-6445
 - Rat, 77-6210
- Skin Neoplasms
 - Carcinogenic Activity, Review, 77-6010
 - Carcinoma, Epidermoid, 77-6042
 - Papilloma, 77-6042
 - Propane, 1,2-Epoxy-3,3,3-trichloro-, 77-6213
- Trace Elements
 - Co-carcinogenic Effect, 77-6216
- Water Pollution

- Benzo(a)pyrene (cont'd)**
Review, 77-6025
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-**
Coliphages
DNA Replication, 77-6208
DNA
Binding, 77-6208
- Benzo(a)pyrene 4,5-Oxide**
Epoxide Hydratases
Metabolism, 77-6061
Hydro-Lyases
Spectrofluorimetric Assay, 77-6207
- 7,8-Benzoflavone**
Benzo(a)pyrene
Colon, 77-6212
DNA, Binding, 77-6204
Metabolism, Rat, 77-6204
Liver
Metabolism, 77-6180
Microsomes
Metabolism, 77-6180
- Benzoic Acid, *p*-Hydroxy-**
Bacteria
Degradation, Review, 77-6062
- p*-Benzoquinone**
Fibrosarcoma
Rat, 77-6049
Lung Neoplasms
Adenocarcinoma, 77-6049
Skin Neoplasms
Carcinoma, 77-6049
Papilloma, 77-6049
- Benzoxazole, 2-Amino-5-chloro-**
Liver
Metabolism, 77-6180
- Benzyl Alcohol, 3,4-Dihydroxy-2-((isopropylamino)methyl)-**
Trachea
Glycoproteins, 77-6070
Goblet Cells, 77-6070
Mucus, 77-6070
- Bile Acids and Salts**
Intestinal Neoplasms
Hydrazine, 1,2-Dimethyl-, 77-6169
Salmonella typhimurium
Mutagenic Activity, 77-6297
- Bilirubin**
Carcinogen, Chemical
Carrier Proteins, 77-6142
- Biphenyl**
Benzene, 4-Allyl-1,2-(methylenedioxy)-
Metabolism, 77-6150
4,4'-Biphenyldiol
Microsomes, Liver, 77-6148
2-Biphenylol
Microsomes, Liver, 77-6148
3-Biphenylol
Microsomes, Liver, 77-6148
4-Biphenylol
Microsomes, Liver, 77-6148
- Biphenyl, 4-Nitroso-**
4-Biphenylamine
Carcinogenic Metabolite, 77-6147
- Biphenyl, Octabromo-**
Thyroid Neoplasms
Precancerous Conditions, Review, 77-6015
- 2-Biphenylamine**
Bladder Neoplasms
Excretion, Dog, 77-6138
Urine
Mutagenic Activity, 77-6138
- 4-Biphenylamine**
Ascorbic Acid
Metabolism, Dog, 77-6147
Biphenyl, 4-Nitroso-
Carcinogenic Metabolite, 77-6147
Hydroxylamine, *N*-4-Biphenyl-
Carcinogenic Metabolite, 77-6147
Skin Neoplasms
Rat, 77-6286
- 4,4'-Biphenyldiol**
Biphenyl
Microsomes, Liver, 77-6148
Microsomes, Liver
Quantitation Method, 77-6148
- 2-Biphenylol**
Benzene, 4-Allyl-1,2-(methylenedioxy)-
Fluorimetric Assay, 77-6150
Biphenyl
Microsomes, Liver, 77-6148
Microsomes, Liver
Quantitation Method, 77-6148
- 3-Biphenylol**
Biphenyl
Microsomes, Liver, 77-6148
Quantitation Method
Microsomes, Liver, 77-6148
- 4-Biphenylol**
Benzene, 4-Allyl-1,2-(methylenedioxy)-
Fluorimetric Assay, 77-6150
Biphenyl
Microsomes, Liver, 77-6148
Microsomes, Liver
Quantitation Method, 77-6148
- Biurea, 1-Methyl-6-(1-methylallyl)-2,5-dithio-**
Pituitary Gland
Histological Study, 77-6537
Ultrastructural Study, 77-6537
- Bladder Neoplasms**
Adenocarcinoma
1-Butanol, 4-(Butylnitrosamino)-, 77-6262
1,2-Benzisothiazolin-3-one, 1,1-Dioxide
Epidemiology, 77-6059
2-Biphenylamine
Excretion, Dog, 77-6138
1-Butanol, 4-(Butylnitrosamino)-
Histological Study, Rat, 77-6261
13-*cis*-Retinoic Acid, 77-6260
Carcinoma
1-Butanol, 4-(Butylnitrosamino)-, 77-6262
Histological Study, 77-6262
Hydroquinone, 77-6042
Carcinoma, Epidermoid
Bracken Fern, 77-6003
1-Butanol, 4-(Butylnitrosamino)-, 77-6003, 77-6262
Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-

Bladder Neoplasms (cont'd)

Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
77-6003

Carcinoma In Situ

1-Butanol, 4-(Butylnitrosamino)-, 77-6261

Carcinoma, Transitional Cell

Bracken Fern, 77-6003

1-Butanol, 4-(Butylnitrosamino)-, 77-6003, 77-6260

77-6261, 77-6262

Cell Line, 77-6534

Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
77-6003

Rat, 77-6260

Chloroform

Epidemiology, 77-6584

Coal

Epidemiology, 77-6582

Coffee

Epidemiology, 77-6059

Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-

Excretion, Dog, 77-6138

Histological Study, 77-6139

Nitrosamines

Urine, Isolation and Characterization, 77-6266

Papilloma

1-Butanol, 4-(Butylnitrosamino)-, 77-6261

Rubber

Epidemiology, 77-6583

Schistosomiasis

Nitrosamines, 77-6266

Smoking

Epidemiology, 77-6059

Tryptophan

Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
77-6139

Metabolism, 77-6140

Tryptophan, 5-Hydroxy-

Review, 77-6060

Urinary Tract Infections

Nitrosamines, 77-6266

Virus, Papova

Antibodies, Viral, 77-6383

Bone and Bones**Plutonium**

Dose-Response Study, 77-6075

Bone Marrow Cells**Leukemia, Myeloblastic**

Cells, Cultured, 77-6561

Leukemia, Myelocytic

Cells, Cultured, 77-6561

Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-

Spermatozoa, 77-6281

Urea, 1-(2-Chloroethyl)-3-(2-hydroxyethyl)-1-nitroso-

Chromosome Aberrations, 77-6281

Bone Neoplasms**Cesium Radioisotopes**

Radiation-Protective Agents, 77-6299

Radiation, Ionizing

Rat, 77-6301

Sarcoma, Osteogenic

Radiation, Ionizing, 77-6301

Strontium Radioisotopes

Radiation-Protective Agents, 77-6299

Brachial Plexus

Thyroid Neoplasms

Brachial Plexus (cont'd)

Nervous System Neoplasms, 77-6543

Bracken Fern**Bladder Neoplasms**

Carcinoma, Epidermoid, 77-6003

Carcinoma, Transitional Cell, 77-6003

Intestinal Neoplasms

Heat Treatment, 77-6177

Histological Study, 77-6177

Brain Neoplasms**Astrocytoma**

Lead, 77-6219

Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-

Carcinogenic Potential, Rat, 77-6156

Hemangiopericytoma

Ultrastructural Study, 77-6547

Lead

Case Report, 77-6219

Meningioma

Ultrastructural Study, 77-6547

Neurilemmoma

Histological Study, 77-6002

Oligodendroglioma

Histological Study, 77-6002

Plants, 77-6173

Plants

Carcinogenic Potential, 77-6173

Urea, 1-Butyl-1-nitroso-

Transplacental Carcinogenesis, 77-6002

Urea, 1,3-Dimethyl-1-nitroso-

Histological Study, 77-6002

Urea, Ethyl Nitroso-

Transplacental Carcinogenesis, 77-6002

Urea, Methyl Nitroso-

Histological Study, 77-6002

Urea, 1,1,3-Trimethyl-3-nitroso-

Histological Study, 77-6002

Breast**Cholesterol**

Epidemiology, 77-6233

Estradiol

Epidemiology, 77-6233

Estrone

Epidemiology, 77-6233

Lipids

Epidemiology, 77-6233

Prolactin

Epidemiology, 77-6233

Breast Feeding**Breast Neoplasms**

Epidemiology, 77-6120

Breast Neoplasms**Adenocarcinoma**

Epidemiology, 77-6574

Age Factors

Epidemiology, Japan, US, 77-6573

Breast Feeding

Epidemiology, 77-6120

Carcinoma

Case Report, 77-6532

Epidemiology, 77-6119, 77-6574

Estradiol, 77-6030

Histological Study, 77-6532

Radiation, Ionizing, 77-6084

Breast Neoplasms (cont'd)

Ultrastructural Study, 77-6532

Diet

Epidemiology, 77-6116, 77-6123, 77-6575

Epidemiology, Review, 77-6124

Epidemiology, 77-6530

Review, 77-6116, 77-6118

Estradiol

Epidemiology, 77-6118

Estriol

Epidemiology, 77-6118

Estrogens, Conjugated

Review, 77-6034

Estrone

Epidemiology, 77-6118

Genetics

Epidemiology, 77-6571

Epidemiology, Review, 77-6115

Histological Study

Epidemiology, 77-6574

Hormones

Epidemiology, 77-6116

Hyperplasia

Precancerous Conditions, 77-6111

Lactation

Epidemiology, 77-6117

T-Lymphocytes

Androgen Sulfates, 77-6531

Myasthenia Gravis

Epidemiology, 77-6531

Precancerous Conditions, 77-6531

Neoplasm Metastasis

Epidemiology, Japan, US, 77-6573

Neoplasms, Multiple Primary

Androgen Sulfates, 77-6531

Myasthenia Gravis, 77-6531

Parity

Epidemiology, 77-6116

Radiation, Ionizing

Epidemiology, 77-6083, 77-6116

Virus, RNA Tumor

Epidemiology, 77-6116

Bronchi**Smoking**

Macrophages, 77-6511

Bronchial Neoplasms**Asbestos**

Epidemiology, 77-6577, 77-6578

Benzo(a)pyrene

Animal Model, Dog, 77-6215

Azathioprine, 77-6215

Precancerous Conditions, 77-6215

Prednisolone, Methyl-, 77-6215

Carcinoma

Asbestos, 77-6577, 77-6578

Immunosuppression

Histological Study, Dog, 77-6215

Mesothelioma

Asbestos, 77-6578

Precancerous Conditions

Animal Model, Dog, 77-6215

Urea, Methyl Nitroso-

Azathioprine, 77-6215

Precancerous Conditions, 77-6215

Prednisolone, Methyl-, 77-6215

Burkitt's Lymphoma**Chromosome Aberrations**

Case Report, 77-6555

B-Lymphocytes

Surface Properties, 77-6565

Virus, Epstein-Barr

Antibodies, Viral, 77-6438

Antigens, Viral, 77-6409, 77-6412, 77-6438

Case Report, 77-6557

B-Lymphocytes, 77-6565

Burns**Carcinoma, Epidermoid**

Cicatrix, 77-6518

Epidemiology, 77-6518

Neoplasm Metastasis, 77-6518

Bursa of Fabricius**Virus, Rous Sarcoma**Estr-4-en-3-one, 7 α ,17-Dimethyl-17 β -Hydroxy
77-6453**1,3-Butadiene, 2-Chloro-****Cell Transformation, Neoplastic**

Lung, Hamster, 77-6159

2,3-Butanediol, 1,4-Dimercapto-**Virus, Polyoma**

Viral Proteins, 77-6381

1-Butanol, 4-(Butylnitrosamino)-**Bladder Neoplasms**

Adenocarcinoma, 77-6262

Carcinoma, 77-6262

Carcinoma, Epidermoid, 77-6003, 77-6262

Carcinoma In Situ, 77-6261

Carcinoma, Transitional Cell, 77-6003, 77-6260

77-6261, 77-6262

Histological Study, Rat, 77-6261

Papilloma, 77-6261

13-*cis*-Retinoic Acid, 77-6260**2-Butene, 1,4-Dichloro-****Salmonella typhimurium**

Mutagenic Activity, 77-6046

Sarcoma

Mouse, 77-6046

Skin Neoplasms

Carcinoma, Epidermoid, 77-6046

Papilloma, 77-6046

Butyric Acid**Virus, Friend Murine Leukemia**

Cell Differentiation, 77-6355

Butyric Acid, 2-Amino-4-(ethylthio)-**Liver**

Metabolism, Rat, 77-6164

RNA, Transfer

Metabolism, Rat, 77-6164

Cadmium**Fibrosarcoma**

Rat, 77-6220

RNA Polymerase

Carcinogenic Potential, 77-6217

Water Pollution

Review, 77-6025

Cadmium Chloride**Diet**

Body Burden, 77-6218

- Cadmium Chloride (cont'd)**
 Toxicity, Dog, 77-6218
 Kidney
 Body Burden, 77-6218
- Caffeine**
 Adrenal Gland Neoplasms
 Adenoma, 77-6290
 Dose-Response Study, Rat, 77-6290
 Methane, Dichloro-, 77-6290
 DNA Repair
 Cell Cycle Kinetics, 77-6291
 Chromatids, 77-6291
 Fibroblasts
 Chromosome Aberrations, 77-6291
 Lymphosarcoma
 Dose-Response Study, Rat, 77-6290
 Methane, Dichloro-, 77-6290
 Mammary Neoplasms, Experimental
 Adenofibroma, 77-6290
 Dose-Response Study, Rat, 77-6290
 Methane, Dichloro-, 77-6290
 Methane, Dichloro-
 Carcinogenic Activity, 77-6290
 Nephroblastoma
 Dose-Response Study, Rat, 77-6290
 Methane, Dichloro-, 77-6290
- Calcium**
 Cesium Radioisotopes
 Cell Transformation, Neoplastic, 77-6299
 Strontium Radioisotopes
 Cell Transformation, Neoplastic, 77-6299
 Virus, Polyoma
 Viral Proteins, 77-6381
- Carbamic Acid, Diethyldithio-**
 Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 DNA, Liver, 77-6254
 Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 DNA, Liver, 77-6254
 Aflatoxin B1
 DNA, Liver, 77-6254
 Dimethylamine, *N*-Nitroso-
 DNA, Liver, 77-6254
 Methanesulfonic Acid, Methyl Ester
 DNA, Liver, 77-6254
 Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)
 DNA, Liver, 77-6254
 Urea, Methyl Nitroso-
 DNA, Liver, 77-6254
- Carbamic Acid, Ethyl Ester**
 Lung Neoplasms
 Adenoma, 77-6162, 77-6163
p-Cresol, 2,6-Di-*tert*-butyl-, 77-6162
 Respiratory Tract Neoplasms
 Ultrastructural Study, Hamster, 77-6267
- Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester**
 Cysteine
 Carcinogenic Activity, Nitrosamides, 77-6284
- Carbon**
 Virus, Rauscher Murine Leukemia
 Cell Transformation, Neoplastic, 77-6466
- Carbon Tetrachloride**
 Water Pollution
 Review, 77-6025
- Carcinoembryonic Antigen**
 Carcinoma, Transitional Cell
 Cells, Cultured, 77-6534
 Colonic Neoplasms
 Transplantation, Heterologous, 77-6503
 Melanoma
 Antibody Specificity, 77-6485
 Cell Membrane, 77-6485
 Isolation and Characterization, 77-6485
 Neoplasms
 Immunosuppression, 77-6099
 Virus, SV40
 Antigens, Viral, 77-6426
- Carcinogen, Chemical**
 Antibody Formation
 Immunosuppression, Review, 77-6100
 Carrier Proteins
 Bilirubin, 77-6142
 Heme, 77-6142
 Metabolism, Liver, 77-6142
 Cell Transformation, Neoplastic
 Screening Methods, Review, 77-6011
 Cells, Cultured
 Metabolism, 77-6298
 Screening, Review, 77-6012
 Cytochrome P-450
 Metabolism, 77-6018
 DNA
 Cell Transformation, Neoplastic, Review, 77-6008
 Mutagenic Activity, Review, 77-6008
 DNA Repair
 Screening Methods, Review, 77-6011
 T-Lymphocytes
 Immunosuppression, Review, 77-6100
 Macrophages
 Immunosuppression, Review, 77-6100
 Mammary Neoplasms, Experimental
 Precancerous Conditions, 77-6111
 Metabolism
 Rat, 77-6198
 Mitochondria
 Oxidative Phosphorylation, 77-6165
 Mutation
 Screening Methods, Review, 77-6011
 Nitrogen Mustard
 Review, 77-6001
 Oxidoreductases
 Review, 77-6009
 Pregnancy
 Metabolism, 77-6198
 Stearic Acid, 12-Hydroxy-
 Oxidative Phosphorylation, 77-6165
 Stearic Acid, 12-Hydroxy-, Methyl Ester
 Oxidative Phosphorylation, 77-6165
- Carcinogen, Environmental**
 Animals, Laboratory
 Risk Evaluation, Review, 77-6020
 Arsenic
 Toxicity, Review, 77-6014
 Carcinoma, Bronchogenic
 Smoking, 77-6019
 Cell Transformation, Neoplastic
 Epidemiology, Review, 77-6114
 Diet
 Epidemiology, 77-6019
 Dose-Response Study

Carcinogen, Environmental (cont'd)

- Risk Evaluation, Review, 77-6020
- Epidemiology
 - Review, 77-6113
- Food Contamination
 - Diethylamine, *N*-Nitroso-, 77-6065
 - Dimethylamine, *N*-Nitroso-, 77-6065
 - Pyrrolidine, 1-Nitroso-, 77-6065
- Genetics
 - Cell Transformation, Neoplastic, 77-6101
 - Immune Response, Review, 77-6102
- Hereditary Diseases
 - Cell Transformation, Neoplastic, 77-6101
- Histological Study
 - Review, 77-6113
- Metals
 - Carcinogenic Potential, 77-6217
 - RNA Polymerase, 77-6217
- Neoplasms
 - Aquatic Animals, Review, 77-6023
- Neoplasms, Multiple Primary
 - Cell Transformation, Neoplastic, 77-6101
- Oncogenic Viruses
 - Co-carcinogenic Activity, Review, 77-6102
- Precancerous Conditions
 - Immune Response, Review, 77-6102
- Respiratory System
 - Immune Response, Review, 77-6017
- Review
 - Toxicology, 77-6113
- Skin Neoplasms
 - Co-carcinogenic Activity, Review, 77-6010
- Smoking
 - Co-carcinogenic Effect, Review, 77-6017
- Water Pollution
 - Fish, 77-6586
 - Legal Aspects, Review, 77-6021

Carcinoma

- Bladder Neoplasms
 - 1-Butanol, 4-(Butylnitrosamino)-, 77-6262
 - Histological Study, 77-6262
 - Hydroquinone, 77-6042
- Breast Neoplasms
 - Case Report, 77-6532
 - Epidemiology, 77-6119, 77-6574
 - Estradiol, 77-6030
 - Histological Study, 77-6532
 - Radiation, Ionizing, 77-6084
 - Ultrastructural Study, 77-6532
- Bronchial Neoplasms
 - Asbestos, 77-6577, 77-6578
- Cervix Neoplasms
 - Epidemiology, Puerto Rico, 77-6572
 - Epidemiology, United States, 77-6572
 - Histocompatibility Antigens, 77-6487
 - Virus, Herpes Simplex 2, 77-6088, 77-6487
- Colonic Neoplasms
 - Diagnosis and Prognosis, 77-6504
 - Epidemiology, 77-6505
 - Polyps, 77-6109
 - Surgery, Operative, 77-6170
- Esophageal Neoplasms
 - Diethylamine, *N*-Nitroso-, 77-6252
- Gastrointestinal Neoplasms
 - Asbestos, 77-6073
- Gynecologic Neoplasms
 - Cell Cycle Kinetics, 77-6576

Carcinoma (cont'd)

- Kidney Neoplasms
 - Dimethylamine, *N*-Nitroso-, 77-6255
 - Laryngeal Neoplasms
 - Asbestos, 77-6073
 - Liver Neoplasms
 - Benzenamine, *N,N*-Dimethyl-4-(3-methylphenyl)azo-, 77-6494
 - Contraceptives, Oral, 77-6238
 - Diethylamine, *N*-Nitroso-, 77-6004
 - Mirex, 77-6050
 - Models, Biological, 77-6004
 - Mycotoxins, 77-6036
 - Virus, Hepatitis, 77-6387
 - Lung Neoplasms
 - Asbestos, 77-6073
 - Mammary Neoplasms, Experimental
 - Acetanilide, 4'-(*p*-Fluorophenyl)-, 77-6134
 - Dog, Review, 77-6038
 - Nasopharyngeal Neoplasms
 - Antibodies, Viral, 77-6404
 - Virus, Epstein-Barr, 77-6404, 77-6412
 - Nose Neoplasms
 - Epidemiology, 77-6579
 - Ovarian Neoplasms
 - Case Report, 77-6525
 - Chromosome Aberrations, 77-6527
 - Histological Study, 77-6525
 - Pancreatic Neoplasms
 - Histological Study, 77-6285
 - Nafenopin, 77-6285
 - Propanol, 1,1'-Iminodi-*N*-nitroso-, 77-6265
 - Ultrastructural Study, 77-6285
 - Parathyroid Neoplasms
 - Genetics, 77-6539
 - Parotid Neoplasms
 - Case Report, 77-6535
 - Ultrastructural Study, 77-6535
 - Propane, 1,2-Dibromo-3-chloro-
 - Mammary Neoplasms, Experimental, 77-6044
 - Propane, 1,2,3-Tris(chloromethoxy)-
 - Mouse, 77-6045
 - Skin Neoplasms
 - p*-Benzoquinone, 77-6049
 - Propane, 1,2,3-Tris(chloromethoxy)-, 77-6045
 - Stomach Neoplasms
 - Diagnosis and Prognosis, 77-6507
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6271
 - Histological Study, 77-6499, 77-6500
 - Ulcer, 77-6501
 - Ultrastructural Study, 77-6499
 - Thyroid Neoplasms
 - Amyloidosis, 77-6542
 - Enzymatic Activity, 77-6542
 - Epidemiology, 77-6540
 - Histological Study, 77-6540
 - Precancerous Conditions, 77-6541
 - Radiation, Ionizing, 77-6083
 - Ultrastructural Study, 77-6542
 - Uterine Neoplasms
 - Estradiol, 77-6030
 - Estrogens, 77-6032, 77-6033
- Carcinoma, Basal Cell**
Xeroderma Pigmentosum
Radiation-Protective Agents, 77-6521

Carcinoma, Bronchogenic

- Carcinogen, Environmental
Smoking, 77-6019
- Culture Media
Cell Line, 77-6509
- Neoplasm Metastasis
Cell Line, 77-6509

Carcinoma, Epidermoid

- Benzene, 1,4-Bis(chloromethoxymethyl)-
Mouse, 77-6043
- Bladder Neoplasms
Bracken Fern, 77-6003
- 1-Butanol, 4-(Butylnitrosamino)-, 77-6003, 77-6262
- Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
77-6003
- Burns
Epidemiology, 77-6518
- Neoplasm Metastasis, 77-6518
- 2-Butene, 1,4-Dichloro-
Skin Neoplasms, 77-6046
- Cervix Neoplasms
Case Report, 77-6524
- Neoplasm Metastasis, 77-6524
- Smoking, 77-6072
- Cicatrix
Burns, 77-6518
- Ear Neoplasms
Sheep, 77-6517
- Esophageal Neoplasms
Ultrastructural Study, Monkey, 77-6508
- Virus-Like Particles, 77-6508
- Ethane, 1,2-Bis(chloromethoxy)-
Mouse, 77-6047
- Head and Neck Neoplasms
Acetic Acid, Ester with 2,6-Dimethyl-*m*-dioxan-4-ol
77-6048
- Lung Neoplasms
Benzo(a)pyrene, 77-6222
- Cholanthrene, 3-Methyl-, 77-6195
- Mouth Neoplasms
Ultrastructural Study, 77-6519
- Neoplasms, Multiple Primary
Case Report, 77-6522
- Propane, 1,2-Dibromo-3-chloro-
Stomach Neoplasms, 77-6044
- Prostatic Neoplasms
Catechol Methyltransferase, 77-6247
- Cholanthrene, 3-Methyl-, 77-6247
- Hydroxyindoleacetic Acid, 77-6247
- Monoamine Oxidase, 77-6247
- Norepinephrine, 77-6247
- Pyrocatechol, 4-(2-Aminoethyl)-, 77-6247
- Serotonin, 77-6247
- Tyrosine Hydroxylase, 77-6247
- Psoriasis
Case Report, 77-6522
- Respiratory Tract Neoplasms
Antigens, Neoplasm, 77-6492
- Ethenamine, *N*-Ethylene-*N*-nitroso-, 77-6248
- 2-Propanol, 1,1'-Iminodi-*N*-nitroso-, 77-6263
- Rat, 77-6492
- Skin Neoplasms
Benzo(a)pyrene, 77-6042
- Models, Biological, 77-6517
- Psoriasis, 77-6522
- Pyrocatechol, 77-6042

Carcinoma, Epidermoid (cont'd)

- 4,4'-Stilbenediol, α,α' -Diethyl-
Cervix Neoplasms, 77-6029
- Stomach Neoplasms
Ethane, 1,2-Dibromo-, 77-6041
- Sweat Gland Neoplasms
Case Report, 77-6520
- Neoplasm Metastasis, 77-6520
- Ultraviolet Rays
Sheep, 77-6517

Carcinoma In Situ

- Bladder Neoplasms
1-Butanol, 4-(Butylnitrosamino)-, 77-6261

Carcinoma, Oat Cell

- Culture Media
Cell Line, 77-6509
- Neoplasm Metastasis
Cell Line, 77-6509

Carcinoma, Papillary

- Thyroid Neoplasms
Neoplasms, Multiple Primary, 77-6543

Carcinoma, Small Cell

- see Carcinoma; Carcinoma, Bronchogenic; Carcinoma,
Oat Cell

Carcinoma, Squamous Cell

- see Carcinoma, Epidermoid

Carcinoma, Transitional Cell

- Acetic Acid, Ester with 2,6-Dimethyl-*m*-dioxan-4-ol
Kidney Neoplasms, 77-6048
- Bladder Neoplasms
Bracken Fern, 77-6003
- 1-Butanol, 4-(Butylnitrosamino)-, 77-6003, 77-6260
77-6261, 77-6262
- Cell Line, 77-6534
- Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
77-6003
- Rat, 77-6260
- Carcinoembryonic Antigen
Cells, Cultured, 77-6534
- Cells, Cultured
Osmolarity, 77-6534
- Glucosephosphate Dehydrogenase
Cells, Cultured, 77-6534
- Corticotropin, 77-6534
- Prostatic Neoplasms
Case Report, 77-6533
- Diagnosis and Prognosis, 77-6533

Carrageen

- Adenocarcinoma
Dose-Response Study, Mouse, 77-6460
- Transplantation Immunology, 77-6460

BCG

- Immunity, Cellular, 77-6461

Corynebacterium parvum

- Immunity, Cellular, 77-6461

Granuloma

- Hydrolases, 77-6289
- Muramidase, 77-6289
- Phagocytes, 77-6289

Virus, Rauscher Murine Leukemia

- Cell Transformation, Neoplastic, 77-6466

- Carrageenan**
see Carrageen
- Carrier Proteins**
Azo Compounds
Metabolism, Liver, 77-6142
Carcinogen, Chemical
Bilirubin, 77-6142
Heme, 77-6142
Metabolism, Liver, 77-6142
- Catechol Methyltransferase**
Prostatic Neoplasms
Carcinoma, Epidermoid, 77-6247
- Cell Adherence**
Lymphoma
Cells, Cultured, 77-6590
- Cell Aggregation**
Kidney Neoplasms
Virus, Lucke Herpes, 77-6567
- Cell Cycle Kinetics**
Caffeine
DNA Repair, 77-6291
Cyclogeximide
DNA Repair, 77-6291
- Cell Differentiation**
Colonic Neoplasms
Transplantation, Heterologous, 77-6503
Cyclophosphamide
B-Lymphocytes, 77-6452
Erythroleukemia
Virus, Friend Murine Leukemia, 77-6355
Hematopoietic Stem Cells
Chick Embryo, 77-6452
Immunosuppression, 77-6452
B-Lymphocytes
Chick Embryo, 77-6452
Immunosuppression, 77-6452
Smoking
Tobacco Supplement, 77-6187
Trachea, Rat, 77-6187
Teratoid Tumor
Virus, SV40, 77-6431
Testosterone
B-Lymphocytes, 77-6452
Virus, Friend Murine Leukemia
Butyric Acid, 77-6355
Hemoglobins, 77-6355
Hypoxanthine, 77-6355
Methane, Sulfinylbis-, 77-6355
- Cell Division**
Colonic Neoplasms
Adenocarcinoma, 77-6171
Hydrazine, 1,1-Dimethyl-, 77-6171
Fibroblasts
Plasminogen Activators, 77-6596
Lymphoma
Cells, Cultured, 77-6590
Neoplasms
Cell Cycle Kinetics, Review, 77-6128
- Cell Membrane**
Anthracene
Lipids, 77-6210
Benzo(a)pyrene
Lipids, 77-6210
- Cell Membrane (cont'd)**
Cell Transformation, Neoplastic
Gap Junctions, 77-6595
Proteins, 77-6313
Ultrastructural Study, 77-6430
Hodgkin's Disease
Surface Properties, 77-6565
Infectious Mononucleosis
Surface Properties, 77-6565
Leukemia, Lymphoblastic
Surface Properties, 77-6565
Mammary Neoplasms, Experimental
Galactosyltransferases, 77-6480
Melanoma
Carcinoembryonic Antigen, 77-6485
Glycoproteins, 77-6589
Phospholipids
Spin Labels, 77-6369
Plasmacytoma
Antigenic Determinants, 77-6479
Receptors, KB-Cell
Isolation and Characterization, 77-6389
Virus, Kirsten Murine Sarcoma
Cell Transformation, Neoplastic, 77-6369
Virus, Rous Sarcoma
Peptides, 77-6307
Virus, SV40
Antigens, Viral, 77-6427
Cell Transformation, Neoplastic, 77-6430, 77-6595
Histocompatibility Antigens, 77-6427
- Cell Migration Inhibition**
Cell Transformation, Neoplastic
Fibroblasts, 77-6598
- Cell Movement**
Cell Transformation, Neoplastic
Cells, Cultured, 77-6597
- Cell Nucleus**
Virus, SV40
Histocompatibility Antigens, 77-6427
- Cell Transformation, Neoplastic**
Aging
Cell Cycle Kinetics, Review, 77-6128
Benzo(a)pyrene
Dose-Response Study, 77-6013
Fluorescamine Labeling, 77-6340
1,3-Butadiene, 2-Chloro-
Lung, Hamster, 77-6159
Carcinogen, Chemical
Screening Methods, Review, 77-6011
Carcinogen, Environmental
Epidemiology, Review, 77-6114
Genetics, 77-6101
Hereditary Diseases, 77-6101
Cell Membrane
Gap Junctions, 77-6595
Proteins, 77-6313
Ultrastructural Study, 77-6430
Cell Movement
Cells, Cultured, 77-6597
Cesium Radioisotopes
Alginate Acid, Sodium Salt, 77-6299
Calcium, 77-6299
Prussian Blue, 77-6299
Cholanthrene, 3-Methyl-
Antigenic Determinants, 77-6481

Cell Transformation, Neoplastic (cont'd)

- Cells, Cultured, 77-6195
- Chromosome Aberrations, 77-6553
- Geldanamycin, 77-6197
- Lung, Fetal, 77-6195
- Chromosome Aberrations
 - Hamster, Chinese, 77-6553
- Dibenz(a,h)anthracene
 - Dose-Response Study, 77-6013
- Diethylamine, *N*-Nitroso-
 - Glucosephosphatase, 77-6253
- DNA Repair
 - Models, Theoretical, 77-6007
- Ethylene, Chloro-
 - Dose-Response Study, 77-6013
- Fibroblasts
 - Cell Migration Inhibition, 77-6598
 - Plasminogen Activators, 77-6596
- Glycoproteins
 - Isolation and Characterization, 77-6129
- Histocompatibility Antigens
 - Antigenic Determinants, Review, 77-6095
- Methotrexate
 - Embryo, Rat, 77-6294
- Methylenediamine, *N,N'*-Dimethyl-*N,N'*-dinitroso-
 - Dose-Response Study, 77-6013
- Neoplasms, Multiple Primary
 - Carcinogen, Environmental, 77-6101
 - Hereditary Diseases, 77-6101
- Nucleotides
 - Hypoxanthine Phosphoribosyltransferase, 77-6595
- Quinoline, 4-Nitro-, 1-Oxide
 - Urea, Hydroxy-, 77-6288
- Strontium Radioisotopes, 77-6299
 - Calcium, 77-6299
 - Prussian Blue, 77-6299
- Teratoid Tumor
 - Virus, SV40, 77-6431
- o*-Toluidine, 4-(*o*-Tolylazo)-
 - Dose-Response Study, 77-6013
- Virus, Adeno 2
 - DNA, Viral, 77-6393
- Virus, Adeno 3
 - Age Factors, 77-6334
- Virus, Adeno 12
 - DNA, Viral, 77-6395, 77-6396
- Virus, Avian Leukosis
 - Antigenic Determinants, 77-6481
 - RNA, Viral, 77-6330
- Virus, Avian Sarcoma
 - Adenosine Cyclic 3',5' Monophosphate, 77-6317
 - Adenyl Cyclase, 77-6317
 - Antigenic Determinants, 77-6481
 - RNA, Viral, 77-6330
- Virus, Epstein-Barr
 - Clone Cells, 77-6405
 - Leukocytes, 77-6405
 - Lymphocytes, 77-6407
 - Uridine, 5-Bromo-2'-deoxy-, 77-6407
- Virus, Friend Murine Leukemia
 - Uridine, 5-Bromo-2'-deoxy-, 77-6153
 - Uridine, 2'-Deoxy-5-iodo-, 77-6153
- Virus, Gross Murine Leukemia
 - T-Lymphocytes, 77-6560
- Virus, Herpes
 - Guinea Pig, 77-6338
- Virus, Herpes Simplex 2

Cell Transformation, Neoplastic (cont'd)

- Hamster, 77-6088
- Virus, Kirsten Murine Sarcoma
 - Cell Membrane, 77-6369
- Virus, Marek's Disease Herpes
 - Virus, Turkey Herpes, 77-6483
- Virus, Moloney Murine Sarcoma
 - Fluorescamine Labeling, 77-6340
- Virus, Murine Mammary Tumor
 - Ergocalciferol, 77-6242
 - Genotype, 77-6372
 - Pregnancy, 77-6372
- Virus, Murine Sarcoma
 - Adenosine Cyclic 3',5' Monophosphate, 77-6368
 - Agglutination, 77-6368
 - Concanavalin A, 77-6368
 - Hexoses, 77-6368
 - Lipids, 77-6368
 - Temperature-Sensitive Mutants, 77-6368
- Virus, Rauscher Murine Leukemia
 - Carbon, 77-6466
 - Carrageen, 77-6466
- Virus, Rous Sarcoma
 - Estr-4-en-3-one, 7 α ,17-Dimethyl-17 β -Hydroxy 77-6453
 - Isolation and Characterization, 77-6307
 - Peptides, 77-6307
 - Phosphatidyl Inositol, 77-6310
 - RNA, Messenger, 77-6313
- Virus, SV40
 - Antigens, Viral, 77-6426
 - Cell Membrane, 77-6430, 77-6595
 - Chromosome Aberrations, 77-6553
 - Contact Inhibition, 77-6588
 - Fluorescamine Labeling, 77-6340
 - Histocompatibility Antigens, 77-6427
 - Hypoxanthine Phosphoribosyltransferase, 77-6595
 - Migration Inhibitory Factor, 77-6464
 - Myosin, 77-6421
 - Nucleotides, 77-6595
- Cells, Cultured
 - Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 - DNA Repair, 77-6005, 77-6303
- Aflatoxin B1
 - Metabolism, 77-6298
- Benzo(a)pyrene
 - Metabolism, 77-6298
 - Mutagenic Activity, Diol Epoxides, 77-6209
- Carcinogen, Chemical
 - Metabolism, 77-6298
 - Screening, Review, 77-6012
- Carcinoma, Transitional Cell
 - Carcinoembryonic Antigen, 77-6534
 - Glucosephosphate Dehydrogenase, 77-6534
 - Osmolarity, 77-6534
- Cell Movement
 - Cell Transformation, Neoplastic, 77-6597
- Cholanthrene, 3-Methyl-
 - Cell Transformation, Neoplastic, 77-6195
- Chromosomes
 - Karyotyping, 77-6516
 - Liver, 77-6516
 - Ploidies, 77-6516
- Dimethylamine, *N*-Nitroso-
 - Metabolism, 77-6298
- Fibroblasts
 - Plasminogen Activators, 77-6596

Cells, Cultured (cont'd)

- Fibrosarcoma
 - Foreign Body Reaction, 77-6497
- Foreign Body Reaction
 - Histological Study, 77-6497
- Guanidine, 1-Methyl-3-nitro-1-nitroso-DNA Repair, 77-6005
- Hodgkin's Disease
 - Antigens, 77-6488
- Hydrazine, 1,2-Dimethyl-Metabolism, 77-6298
- Interferon
 - Virus, Murine Mammary Tumor, 77-6375
- Leukemia
 - Cytotoxicity Tests, Immunologic, 77-6437
 - Guinea Pig, 77-6090, 77-6091
 - Immunity, Cellular, 77-6434
- Leukemia, Myeloblastic
 - Bone Marrow Cells, 77-6561
 - Chromosome Aberrations, 77-6562
 - Hematopoietic Stem Cells, 77-6591
- Leukemia, Myelocytic
 - Bone Marrow Cells, 77-6561
- Lung Neoplasms
 - Cholanthrene, 3-Methyl-, 77-6195
- Lymphoma
 - Cell Adherence, 77-6590
 - Cell Division, 77-6590
 - Cytotoxicity Tests, Immunologic, 77-6437
- Mammary Neoplasms, Experimental
 - Immune Response, 77-6443
- Melanoma
 - Glycoproteins, 77-6589
- Methanesulfonic Acid, Methyl Ester
 - DNA Repair, 77-6005
- Radiation, Ionizing
 - Cell Cycle Kinetics, 77-6304
 - DNA Replication, 77-6304
- Sarcoma
 - Cytotoxicity Tests, Immunologic, 77-6437
- Ultraviolet Rays
 - DNA Repair, 77-6303
- Virus, Adeno 2
 - Receptors, KB-Cell, 77-6389
- Virus, Avian Sarcoma
 - RNA, Viral, 77-6311
 - Viral Proteins, 77-6308
- Virus, C-Type RNA Tumor
 - Antigens, Viral, 77-6349
 - Genetics, 77-6343
 - Virus Replication, 77-6349
- Virus, Epstein-Barr
 - Lymphocytes, 77-6406
- Virus, Friend Murine Leukemia
 - Isolation and Characterization, 77-6350
- Virus, Guinea Pig Herpes-Like
 - Ultrastructural Study, 77-6090
- Virus, Guinea Pig RNA Tumor
 - Ultrastructural Study, 77-6090
- Virus, Herpes Simplex 1
 - Antigens, Viral, 77-6397
 - Chromosome Aberrations, 77-6399
 - DNA, Viral, 77-6398
- Virus, Herpes Simplex 2
 - Antigens, Viral, 77-6397
 - Chromosome Aberrations, 77-6399
 - Thymidine Kinase, 77-6402

Cells, Cultured (cont'd)

- Ultrastructural Study, 77-6400
- Virus-Like Particles
 - Isolation and Characterization, 77-6339
 - Reverse Transcriptase, 77-6339
- Virus, Moloney Murine Leukemia
 - Isolation and Characterization, 77-6350
- Virus, Murine Leukemia
 - Geldanamycin, 77-6197
 - Isolation and Characterization, 77-6350
 - Leukemia, 77-6354
- Virus, Murine Mammary Tumor
 - Isolation and Characterization, 77-6374
 - Ultrastructural Study, 77-6374
- Virus, RNA Tumor
 - Virus Replication, 77-6326
- Virus, Rous-Associated
 - RNA, Viral, 77-6316
- Virus, Rous Sarcoma
 - RNA, Viral, 77-6316
 - Virus, Rous-Associated, 77-6308
- Virus, Sindbis
 - Virus Replication, 77-6326
- Virus, SV40
 - DNA Polymerase, 77-6424
- Xeroderma Pigmentosum
 - Chromosome Aberrations, 77-6287

Cellular Inclusions

- Smoking
 - Macrophages, 77-6192

Cervix Neoplasms

- Carcinoma
 - Epidemiology, Puerto Rico, 77-6572
 - Epidemiology, United States, 77-6572
 - Histocompatibility Antigens, 77-6487
 - Virus, Herpes Simplex 2, 77-6487
- Carcinoma, Epidermoid
 - Case Report, 77-6524
 - Neoplasm Metastasis, 77-6524
 - Smoking, 77-6072
- Histocompatibility Antigens
 - Epidemiology, 77-6487
- Neoplasm Metastasis
 - Epidemiology, Puerto Rico, 77-6572
 - Epidemiology, United States, 77-6572
- Smoking
 - Epidemiology, 77-6072
 - Models, Theoretical, 77-6072
- 4,4'-Stilbenediol, α,α' -Diethyl-Carcinoma, Epidermoid, 77-6029
- Review, 77-6029
- Virus, Herpes Simplex 2
 - Carcinoma, 77-6088
 - Epidemiology, 77-6487
 - Epidemiology, Review, 77-6089

Cervix Uteri

- Toxoplasma gondii*
 - Case Report, 77-6074

Cesium Radioisotopes

- Alginate Acid, Sodium Salt
 - Cell Transformation, Neoplastic, 77-6299
- Bone Neoplasms
 - Radiation-Protective Agents, 77-6299
- Calcium
 - Cell Transformation, Neoplastic, 77-6299

- Cesium Radioisotopes (cont'd)**
 Prussian Blue
 Cell Transformation, Neoplastic, 77-6299
- Chlorine**
 Water Pollution
 Carcinogenic Potential, Review, 77-6026
- Chloroform**
 Bladder Neoplasms
 Epidemiology, 77-6584
 Colon Neoplasms
 Epidemiology, 77-6584
 Lung Neoplasms
 Epidemiology, 77-6584
 Toxicology
 Genetics, 77-6155
 Water Pollutants
 Toxicology, 77-6155
 Water Pollution
 Carcinogenic Potential, 77-6027
 Epidemiology, 77-6584
- 5 β -Cholan-24-oic Acid, 3 α -Hydroxy-2-Anthracenamide**
 Mutagenic Activity, 77-6297
Salmonella typhimurium
 Mutagenic Activity, 77-6297
- Cholangiocarcinoma**
 see Cholangioma
- Cholangioma**
 Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
 Antigens, Neoplasm, 77-6494
 Liver Neoplasms
 2-Propanol, 1,1'-Iminodi-*N*-nitroso-, 77-6264
 77-6265
 Urea, Methyl Nitroso-, 77-6277
- Cholanthrene, 3-Methyl-**
 Antibody Formation
 Strain Difference, Mouse, 77-6196
 Antigenic Determinants
 Cell Transformation, Neoplastic, 77-6481
 Aryl Hydrocarbon Hydroxylases
 Enzymatic Activity, 77-6198
 Enzymatic Activity, Hamster, Rat, 77-6194
 Cell Transformation, Neoplastic
 Cells, Cultured, 77-6195
 Geldanamycin, 77-6197
 Lung, Fetal, 77-6195
 Chromosome Aberrations
 Cell Transformation, Neoplastic, 77-6553
 Dimethylamine, *N*-Nitroso-
 Alkylation and Demethylation, 77-6258
 Fibrosarcoma
 Lymphatic Metastasis, 77-6599
 Peptidoglycan, 77-6459
 Uridine, 5-Bromo-2'-deoxy-, 77-6153
 Uridine, 2'-Deoxy-5-iodo-, 77-6153
 Histocompatibility Antigens
 Transplantation Immunology, 77-6448, 77-6493
 Immunosuppression
 Strain Difference, Mouse, 77-6196
 Lung Neoplasms
 Carcinoma, Epidermoid, 77-6195
 Cells, Cultured, 77-6195
 Precancerous Conditions, 77-6195
 Lymphoma
- Cholanthrene, 3-Methyl- (cont'd)**
 Transplantation Immunology, 77-6455
 Mammary Neoplasms, Experimental
 Histological Study, 77-6528
 Neoplasms, Experimental
 Antigens, Neoplasm, 77-6099
 T-Lymphocytes, 77-6448
 Transplantation Immunology, 77-6448
 Prostatic Neoplasms
 Biogenic Amines, 77-6247
 Carcinoma, Epidermoid, 77-6247
 Respiratory Tract Neoplasms
 Antigens, Neoplasm, 77-6492
Salmonella typhimurium
 Mutagenic Activity, 77-6198
 Sarcoma
 Antigenic Determinants, 77-6493
 Antigens, Neoplasm, 77-6490
 T-Lymphocytes, 77-6451
 Transplantation Immunology, 77-6451
 Virus, Avian Sarcoma
 Immunity, Cellular, 77-6481
- Cholesterol**
 Breast
 Epidemiology, 77-6233
 Colonic Neoplasms
 Diet, 77-6122
 Gastrointestinal Neoplasms
 Diet, 77-6122
 Leukemia
 Lymphocytes, 77-6592
 Metabolism
 Review, 77-6037
 Plant Agglutinins
 Lymphocytes, 77-6592
- Chromatids**
 Caffeine
 DNA Repair, 77-6291
 Cycloheximide
 DNA Repair, 77-6291
- Chromatin**
 Antigens, Viral
 Isolation and Characterization, 77-6410
- Chromosome Aberrations**
 Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 Xeroderma Pigmentosum, 77-6287
 Burkitt's Lymphoma
 Case Report, 77-6555
 Caffeine
 Fibroblasts, 77-6291
 Cell Transformation, Neoplastic
 Hamster, Chinese, 77-6553
 Cholanthrene, 3-Methyl-
 Cell Transformation, Neoplastic, 77-6553
 Colonic Neoplasms
 Polyps, 77-6506
 Cycloheximide
 Fibroblasts, 77-6291
 Daunomycin
 Xeroderma Pigmentosum, 77-6287
 Ethyl Alcohol
 Lymphocytes, 77-6181
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 Embryo, Hamster, 77-6272
 G-Banding, 77-6272

Chromosome Aberrations (cont'd)

- Xeroderma Pigmentosum, 77-6287
- Leukemia
 - Review, 77-6106
- Leukemia, Myeloblastic
 - Cells, Cultured, 77-6562
- Lymphoma, Giant Follicular
 - Case Report, 77-6554
 - Chromosomes, Human, 13-15, 77-6554
- Mitomycin
 - Mouse, 77-6292
- Neoplasms
 - Review, 77-6107
- Neoplasms, Experimental
 - Review, 77-6107
- Ovarian Neoplasms
 - Carcinoma, 77-6527
- Quinoline, 4-Nitro-, 1-Oxide
 - Xeroderma Pigmentosum, 77-6287
- Radiation, Ionizing
 - Lymphocytes, 77-6078
- Retinoblastoma
 - Epidemiology, 77-6552
- Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
 - Spermatozoa, 77-6281
- Urea, 1-(2-Chloroethyl)-3-(2-hydroxyethyl)-1-nitroso-
 - Bone Marrow Cells, 77-6281
 - Spermatozoa, 77-6281
- Virus, Herpes Simplex 1
 - Cells, Cultured, 77-6399
- Virus, Herpes Simplex 2
 - Cells, Cultured, 77-6399
- Virus, SV40
 - Cell Transformation, Neoplastic, 77-6553
- Xeroderma Pigmentosum
 - Cells, Cultured, 77-6287

Chromosome Abnormalities

- Aspergillus parasiticus*
 - Lymphocytes, 77-6176
 - Mycotoxins, 77-6176
- Leukemia
 - Precancerous Conditions, Review, 77-6105
- Leukemia, Lymphocytic
 - Chromosomes, Human, 1-3, 77-6558
 - Chromosomes, Human, 6-12, 77-6558

Chromosomes

- Cells, Cultured
 - Karyotyping, 77-6516
 - Ploidies, 77-6516
- Ethyl Alcohol
 - Mutagenic Activity, 77-6181
- Leukemia
 - Urea, Ethyl Nitroso-, 77-6279
- Liver
 - Cells, Cultured, 77-6516
- Virus, Herpes Simplex 2
 - Thymidine Kinase, 77-6402

Chromosomes, Human, 1-3

- Leukemia, Lymphocytic
 - Chromosome Abnormalities, 77-6558

Chromosomes, Human, 13-15

- Lymphoma, Giant Follicular
 - Chromosome Aberrations, 77-6554

Chromosomes, Human, 6-12

- Leukemia, Lymphocytic
 - Chromosome Abnormalities, 77-6558

Chrysene

- Carcinogenic Potential
 - Models, Theoretical, 77-6201
- Salmonella typhimurium*
 - Mutagenic Activity, 77-6202

Chrysene, 1,2-Dihydro-1,2-dihydroxy-

- Enzyme Activation
 - Mutagenic Activity, 77-6202
- Microsomes, Liver
 - Mutagenic Activity, 77-6202
- Salmonella typhimurium*
 - Mutagenic Activity, 77-6202

Chrysene, 3,4-Dihydro-3,4-dihydroxy-

- Salmonella typhimurium*
 - Mutagenic Activity, 77-6202

Chrysene, 5,6-Dihydro-1,2-dihydroxy-

- Salmonella typhimurium*
 - Mutagenic Activity, 77-6202

Chrysene, 5-Methyl-

- Neoplasms
 - Epidemiology, 77-6200

Cicatrix

- Carcinoma, Epidermoid
 - Burns, 77-6518

Coal

- Bladder Neoplasms
 - Epidemiology, 77-6582
- Colonic Neoplasms
 - Epidemiology, 77-6582
- Kidney Neoplasms
 - Epidemiology, 77-6582
- Lung Neoplasms
 - Benzo(a)pyrene, 77-6582
 - Epidemiology, 77-6582
- Rectal Neoplasms
 - Epidemiology, 77-6582

Cobalt

- RNA Polymerase
 - Carcinogenic Potential, 77-6217

Coliphages

- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-
 - DNA Replication, 77-6208

Colon

- Benzo(a)pyrene
 - Aryl Hydrocarbon Hydroxylases, 77-6212
 - Benz(a)anthracene, 77-6212
 - 7,8-Benzoflavone, 77-6212
 - Carcinogenic Metabolite, 77-6212
 - Disulfide, Bis(diethylthiocarbamoyl)-, 77-6212
 - DNA, Binding, 77-6212

Colon Neoplasms

- Chloroform
 - Epidemiology, 77-6584

Colonic Neoplasms

- Adenocarcinoma
 - Cell Division, 77-6171

- Colonic Neoplasms (cont'd)**
 Hydrazine, 1,1-Dimethyl-, 77-6171
 Naphthalene, 1-Nitroso-, 77-6286
 Transplantation, Heterologous, 77-6503
- Carcinoma**
 Diagnosis and Prognosis, 77-6504
 Epidemiology, 77-6505
 Polyps, 77-6109
 Surgery, Operative, 77-6170
- Coal**
 Epidemiology, 77-6582
- Diet**
 Cholesterol, 77-6122
 Epidemiology, 77-6123
- Epithelial Cells**
 Ultrastructural Study, Rat, 77-6566
- Hodgkin's Disease**
 Enteritis, Regional, 77-6564
- Hydrazine, 1,1-Dimethyl-**
 Cell Division, 77-6171
 Resection, Small Intestine, 77-6170
 Surgery, Operative, 77-6170
- Hydrazine, 1,2-Dimethyl-**
 Ultrastructural Study, Rat, 77-6566
- Neoplasms, Multiple Primary**
 Genetics, 77-6506
- Polyps**
 Chromosome Aberrations, 77-6506
 Genetics, 77-6506
- Precancerous Conditions**
 Histological Study, 77-6502
- Transplantation, Heterologous**
 Carcinoembryonic Antigen, 77-6503
 Cell Differentiation, 77-6503
 Phenotype, 77-6503
- Complement**
 Lymphoma
 Lymphocytes, 77-6471
 Lymphoma, Lymphocytic
 Lymphocytes, 77-6471
 Virus, Adeno 7 - SV40 Hybrid
 Antigen-Antibody Reactions, 77-6439
- Concanavalin A**
 Smoking
 Macrophages, 77-6192
 Virus, Murine Sarcoma
 Cell Transformation, Neoplastic, 77-6368
- Contraceptives, Oral**
 Liver Neoplasms
 Adenoma, 77-6036, 77-6237
 Carcinoma, 77-6238
 Case Report, 77-6238
 Pregnancy, 77-6238
 Mammary Neoplasms, Experimental
 Dog, Review, 77-6038
 DU 41274, 77-6239
 4,4'-Stilbenediol, α,α' -Diethyl-
 Teratogenic Activity, 77-6028
- Copper**
 RNA Polymerase
 Carcinogenic Potential, 77-6217
- Corticotropin**
 Aflatoxin B1
 Carcinogenic Activity, Rat, 77-6174
 Carcinoma, Transitional Cell
- Corticotropin (cont'd)**
 Glucosephosphate Dehydrogenase, 77-6534
 Hepatoma
 Aflatoxin B1, 77-6174
 Lymphoma
 Aflatoxin B1, 77-6174
- Corynebacterium parvum***
 Carrageen
 Immunity, Cellular, 77-6461
 Fibrosarcoma
 Benz(a)anthracene, 7,12-Dimethyl-, 77-6461
 Immunity, Cellular, 77-6461
 Transplantation Immunology, 77-6444
 Silica, Crystalline
 Immunity, Cellular, 77-6461
- Coumarin**
 Liver
 Metabolism, 77-6180
- Coumarin, 7-Ethoxy-**
 Liver
 Metabolism, 77-6180
- Creatine Kinase**
 Teratoid Tumor
 Virus, SV40, 77-6431
- p*-Cresol, 2,6-Di-*tert*-butyl-**
 Lung Neoplasms
 Carbamic Acid, Ethyl Ester, 77-6162
- Cyclohexane, 1,2,3,4,5,6-Hexachloro-, γ -Isomer**
 Benzo(a)pyrene
 Carcinogenic Metabolite, 77-6205
- Cycloheximide**
 DNA Repair
 Cell Cycle Kinetics, 77-6291
 Chromatids, 77-6291
 Fibroblasts
 Chromosome Aberrations, 77-6291
 Proteins
 Degradation, Intracellular, 77-6588
 Virus, Murine Leukemia
 RNA Replication, 77-6367
 Virus, Murine Sarcoma
 RNA Replication, 77-6367
- Cyclophosphamide**
 B-Lymphocytes
 Cell Differentiation, 77-6452
 Chick Embryo, 77-6452
 Virus, Avian Leukosis
 B-Lymphocytes, 77-6467
- Cylindroma**
 Neoplasms, Multiple Primary
 Ultrastructural Study, 77-6523
 Skin Neoplasms
 Ultrastructural Study, 77-6523
- Cysteine**
 Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester
 Carcinogenic Activity, Nitrosamides, 77-6284
 Propionamide, *N*-Methyl-*N*-nitroso-
 Carcinogenic Activity, Nitrosamides, 77-6284
 Urea, Methyl Nitroso-
 Carcinogenic Activity, Nitrosamides, 77-6284
- Cytochalasin B**
 Lymphoid Tissue

- Cytochalasin B (cont'd)**
Rosette Formation, Chick, 77-6472
- Cytochrome P-450**
Acetamide, *N*-Fluoren-2-yl-
Metabolism, 77-6018
Acetanilide, 4'-Hydroxy-
Metabolism, 77-6018
Benzo(a)pyrene
Metabolism, 77-6018
Carcinogen, Chemical
Metabolism, 77-6018
Dimethylamine, *N*-Nitroso-
Drugs, 77-6258
Metabolism, 77-6259
Ellipticine
DNA, Binding, 77-6206
Microsomes, Liver, 77-6206
Genetics
Metabolism, 77-6018
- Cytochromes**
Ellipticine
Microsomes, Liver, 77-6206
- Cytoplasm**
RNA
Liver Regeneration, 77-6593
- Cytotoxicity Tests, Immunologic**
Leukemia
Cells, Cultured, 77-6437
Lymphoma
Cells, Cultured, 77-6437
Sarcoma
Cells, Cultured, 77-6437
- Daunomycin**
Chromosome Aberrations
Xeroderma Pigmentosum, 77-6287
DNA Repair
Spleen, Rat, 77-6293
Ultraviolet Rays
DNA Repair, 77-6293
- Dexamethasone**
Virus, Kirsten Murine Sarcoma
Reverse Transcriptase, 77-6370
- Dibenz(a,h)anthracene**
Cell Transformation, Neoplastic
Dose-Response Study, 77-6013
- Dibenzo-*p*-dioxin**
Liver Neoplasms
Mouse, 77-6040
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-**
Brain Neoplasms
Carcinogenic Potential, Rat, 77-6156
Kidney Neoplasms
Carcinogenic Potential, Rat, 77-6156
Liver Neoplasms
Carcinogenic Potential, Rat, 77-6156
Epidemiology, 77-6040
Mouse, 77-6040
Lung Neoplasms
Carcinogenic Potential, Rat, 77-6156
Dose-Response Study, 77-6156
Skin Neoplasms
Carcinogenic Potential, Rat, 77-6156
Testicular Neoplasms
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro- (cont'd)**
Carcinogenic Potential, Rat, 77-6156
- Dichromic Acid, Dipotassium Salt**
DNA Replication
Fibroblasts, Hamster, 77-6221
- Diet**
Aramite
Metabolism, Rat, 77-6160
Breast Neoplasms
Epidemiology, 77-6116, 77-6123, 77-6575
Epidemiology, Review, 77-6124
Cadmium Chloride
Body Burden, 77-6218
Toxicity, Dog, 77-6218
Carcinogen, Environmental
Epidemiology, 77-6019
Colonic Neoplasms
Cholesterol, 77-6122
Epidemiology, 77-6123
Digestive System Neoplasms
Epidemiology, Review, 77-6124
Esophageal Neoplasms
Epidemiology, 77-6569
Gastrointestinal Neoplasms
Cholesterol, 77-6122
Intestinal Neoplasms
Epidemiology, 77-6569
Hydrazine, 1,2-Dimethyl-, 77-6169
Oxprenolol
Carcinogenic Potential, Mouse, 77-6241
Prostatic Neoplasms
Epidemiology, 77-6123
Rectal Neoplasms
Epidemiology, 77-6123, 77-6569
Stomach Neoplasms
Epidemiology, 77-6123, 77-6569
- Dietary Fats**
Intestinal Neoplasms
Epidemiology, Review, 77-6121
Hydrazine, 1,2-Dimethyl-, 77-6121
Mammary Neoplasms, Experimental
Estrogens, 77-6234
Prolactin, 77-6234
Urea, Methyl Nitroso-, 77-6234
- Diethylamine, *N*-Nitroso-**
Esophageal Neoplasms
Carcinoma, 77-6252
Histological Study, Rat, 77-6252
Precancerous Conditions, 77-6252
Food Contamination
Carcinogen, Environmental, 77-6065
Glucosephosphatase
Cell Transformation, Neoplastic, 77-6253
Liver, Rat, 77-6253
Glucosephosphate
Liver, Rat, 77-6251
Hepatoma
Histological Study, Fish, 77-6249
• Temperature, 77-6249
Liver Neoplasms
Barbituric Acid, 5-Ethyl-5-phenyl-, 77-6004
Carcinoma, 77-6004
Dose-Response Study, 77-6250
Precancerous Conditions, 77-6251
Progesterone, 77-6236

Diethylamine, N-Nitroso- (cont'd)

- Liver, Rat
 - Phosphates, 77-6251
- Metabolism
 - Carcinogenic Activity, 77-6063
 - Mutagenic Activity, 77-6063
- Nitrous Acid
 - Carcinogenic Activity, 77-6063
 - Mutagenic Activity, 77-6063
- Respiratory Tract Neoplasms
 - Hamster, 77-6214
 - Ultrastructural Study, Hamster, 77-6267

Digestive System Neoplasms

- Adenocarcinoma
 - Carcinogenic Potential, Hamster, 77-6248
- Bracken Fern
 - Epidemiology, Cattle, 77-6178
- Diet
 - Epidemiology, Review, 77-6124
- Virus, Papilloma
 - Epidemiology, Cattle, 77-6178

Dimethylamine, N-Nitroso-

- Barbituric Acid, 5-Ethyl-5-phenyl-
 - 1-Propanone, 2-Methyl-1,2-di-3-pyridyl-, Tartrate 77-6258
- Carbamic Acid, Diethyldithio-
 - DNA, Liver, 77-6254
- Cells, Cultured
 - Metabolism, 77-6298
- Cholanthrene, 3-Methyl-
 - Alkylation and Demethylation, 77-6258
- Cytochrome P-450
 - Drugs, 77-6258
 - Metabolism, 77-6259
- DNA Repair
 - Rat, 77-6257
- DNA Replication
 - Hepatectomy, Rat, 77-6256
- Fatty Acids
 - Metabolism, 77-6259
- Food Contamination
 - Carcinogen, Environmental, 77-6065
- Gastrointestinal Neoplasms
 - Carcinogenic Activity, 77-6069
- Glycinonitrile
 - DNA, Liver, 77-6254
- Kidney Neoplasms
 - Adenoma, 77-6255
 - Carcinogenic Activity, 77-6069
 - Carcinoma, 77-6255
 - Orchiectomy, Mouse, 77-6255
- Liver Neoplasms
 - Carcinogenic Activity, 77-6069
- Liver Regeneration
 - DNA Replication, 77-6256
- Metabolism
 - Carcinogenic Activity, 77-6063, 77-6069
 - Mutagenic Activity, 77-6063, 77-6069
- Models, Theoretical
 - Carcinogenic Potential, 77-6268
- Nitrous Acid
 - Carcinogenic Activity, 77-6063
 - Mutagenic Activity, 77-6063
- Oxidoreductases
 - Review, 77-6009
- 1-Propanone, 2-Methyl-1,2-di-3-pyridyl-, Tartrate

Dimethylamine, N-Nitroso- (cont'd)

- Alkylation and Demethylation, 77-6258
- Respiratory Tract Neoplasms
 - Carcinogenic Activity, 77-6069
 - Ultrastructural Study, Hamster, 77-6267
- Stomach Neoplasms
 - Epidemiology, 77-6064
- Valeric Acid, 2,2-Diphenyl-, 2-(Diethylamino)ethyl Ester HCl
 - 1-Propanone, 2-Methyl-1,2-di-3-pyridyl-, Tartrate 77-6258

Dipyridamole

- Neoplasm Metastasis
 - Platelet Aggregation, 77-6549

Disgerminoma

- Ovarian Neoplasms
 - Histological Study, Fish, 77-6526

Disulfide, Bis(diethylthiocarbamoyl)-

- Benzo(a)pyrene
 - Colon, 77-6212

Disulfiram

- see Disulfide, Bis(diethylthiocarbamoyl)

Diterpenes

- Plants
 - Isolation and Characterization, Review, 77-6053

Dithiothreitol

- see 2,3-Butanediol, 1,4-Dimercapto-

DNA

- Acetic Acid, (N-Acetyl-N-2-phenanthryl)amino) Ester
 - Acetylation and Phenanthrylation, 77-6137
 - Modification, Structural, 77-6137
- Adenine, 1-(2-Carboxyethyl)-
 - 2-Oxetanone, 77-6240
- Benzo(a)pyrene
 - Enzymatic Activity, 77-6182
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-
 - Binding, 77-6208
- Carcinogen, Chemical
 - Cell Transformation, Neoplastic, Review, 77-6008
 - Mutagenic Activity, Review, 77-6008
- DNA, Viral
 - Binding, 77-6378
- Ethyl Alcohol
 - Aryl Hydrocarbon Hydroxylases, 77-6182
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Mutagenic Activity, 77-6067
- Leukemia
 - Urea, Ethyl Nitroso-, 77-6279
- Nitric Acid
 - Mutagenic Activity, 77-6067
- Nitrous Acid
 - Mutagenic Activity, 77-6067
- 2-Oxetanone
 - Adenine Derivatives, 77-6240
 - Binding, Liver, Thymus, 77-6240
- Urea, Methyl Nitroso-
 - Escherichia coli*, 77-6278
 - Purine, 2-Amino-6-methoxy-, 77-6276
- Viral Proteins
 - Binding, 77-6366, 77-6371, 77-6394
- Virus, Adeno 5
 - Viral Proteins, 77-6394
- Virus, SV40

DNA (cont'd)

Base Sequence, 77-6417

DNA, Bacterial

Agrobacterium tumefaciens

Isolation and Characterization, 77-6131

Plant Tumors

Agrobacterium tumefaciens, 77-6131

DNA Nucleotidyltransferases

DNA Repair

Enzymatic Activity, 77-6130

DNA Polymerase

Virus Replication

Isolation and Characterization, 77-6424

Virus, SV40

Cells, Cultured, 77-6424

Virus Replication, 77-6424

DNA Repair

Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-

Cells, Cultured, 77-6005, 77-6303

Xeroderma Pigmentosum, 77-6287

Caffeine

Cell Cycle Kinetics, 77-6291

Chromatids, 77-6291

Carcinogen, Chemical

Screening Methods, Review, 77-6011

Cell Transformation, Neoplastic

Models, Theoretical, 77-6007

Cycloheximide

Cell Cycle Kinetics, 77-6291

Chromatids, 77-6291

Daunomycin

Spleen, Rat, 77-6293

Dimethylamine, *N*-Nitroso-

Rat, 77-6257

DNA Nucleotidyltransferases

Enzymatic Activity, 77-6130

Endonucleases

Enzymatic Activity, 77-6130

Exonucleases

Enzymatic Activity, 77-6130

Guanidine, 1-Methyl-3-nitro-1-nitroso-

Cells, Cultured, 77-6005

Xeroderma Pigmentosum, 77-6287

Methanesulfonic Acid, Methyl Ester

Cells, Cultured, 77-6005

Rat, 77-6257

Methotrexate

Spleen, Rat, 77-6293

Purine-6-thiol

Spleen, Rat, 77-6293

Quinoline, 4-Nitro-, 1-Oxide

Urea, Hydroxy-, 77-6288

Xeroderma Pigmentosum, 77-6287

Serine, Diazoacetate (Ester)

Dose-Response Study, 77-6167

Kidney, Liver, Pancreas, Rat, 77-6167

Ultraviolet Rays

Cells, Cultured, 77-6303

Daunomycin, 77-6293

Mitomycin C, 77-6293

Purine-6-thiol, 77-6293

Spleen, Rat, 77-6293

Uracil, 5-Fluoro-, 77-6293

Uracil, 5-Fluoro-

Spleen, Rat, 77-6293

DNA Replication

Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-

Coliphages, 77-6208

Dichromic Acid, Dipotassium Salt

Fibroblasts, Hamster, 77-6221

Dimethylamine, *N*-Nitroso-

Hepatectomy, Rat, 77-6256

Liver Regeneration, 77-6256

Hodgkin's Disease

Lymphocytes, 77-6473

Leukemia

Lymphocytes, 77-6592

Lymphocyte Transformation

Inhibitory Factor, Isolation and Characterization
77-6469

B-Lymphocytes

Schistosoma mansoni, 77-6469

T-Lymphocytes

Schistosoma mansoni, 77-6469

Plant Agglutinins

Lymphocytes, 77-6592

Radiation, Ionizing

Cells, Cultured, 77-6304

Virus, Avian Myeloblastosis

Reverse Transcriptase, 77-6321

Virus, Epstein-Barr

Lymphocytes, 77-6407

Virus, SV40

Antigens, Viral, 77-6419

Temperature Sensitive Mutants, 77-6420

DNA, Viral

DNA

Binding, 77-6378

DNA-RNA Hybridization

Ultrastructural Study, 77-6392

Nasopharyngeal Neoplasms

Nucleic Acid Hybridization, 77-6404

Virus, Adeno

Isolation and Characterization, 77-6335

Mouse FL Strain, 77-6335

Virus, Adeno 2

Cell Transformation, Neoplastic, 77-6393

Isolation and Characterization, 77-6390

RNA, Messenger, 77-6392

Virus, Adeno 12

Cell Transformation, Neoplastic, 77-6395, 77-6396

Virus, Avian Myeloblastosis

DNA-RNA Hybridization, 77-6318

Virus Replication, 77-6318

Virus, B77

Binding Sites, 77-6309

DNA-RNA Hybridization, 77-6309

Virus, Epstein-Barr

Clone Cells, 77-6405

Virus, Herpes Simplex 1

Carcinogenic Potential, Review, 77-6089

Cells, Cultured, 77-6398

Nucleic Acid Hybridization, 77-6398

Virus, Herpes Simplex 2

Carcinogenic Potential, Review, 77-6089

Virus, Murine Mammary Tumor

Isolation and Characterization, 77-6376

Virus, Papilloma

Isolation and Characterization, 77-6386

Reassociation Kinetics, 77-6386

Ultrastructural Study, 77-6386

DNA, Viral (cont'd)

Warts, 77-6386

Virus, Polyoma

DNA-RNA Hybridization, 77-6380

Mouse, 77-6378

RNA Replication, 77-6380

Ultrastructural Study, 77-6416

Virus, Rous Sarcoma

Binding Sites, 77-6309

DNA-RNA Hybridization, 77-6309

Virus, SV40

Genetics, 77-6433

Isolation and Characterization, 77-6419

RNA Polymerase, 77-6425

Ultrastructural Study, 77-6416, 77-6418

DU 41274**Mammary Neoplasms, Experimental**

Adenoma, 77-6239

Contraceptives, Oral, 77-6239

Hyperplasia, 77-6239

Ear Neoplasms**Carcinoma, Epidermoid**

Sheep, 77-6517

Ellipticine**Cytochrome P-450**

DNA, Binding, 77-6206

Microsomes, Liver, 77-6206

Cytochromes

Microsomes, Liver, 77-6206

Hydroxylases

Microsomes, Liver, 77-6206

Endocytosis***Mycobacterium bovis***

Erythrocytes, 77-6462

Hemoglobins, 77-6462

Macrophages, 77-6462

Toxoplasma gondii

Erythrocytes, 77-6462

Hemoglobins, 77-6462

Macrophages, 77-6462

Endonucleases**DNA Repair**

Enzymatic Activity, 77-6130

Enteritis, Regional**Colonic Neoplasms**

Hodgkin's Disease, 77-6564

Hodgkin's Disease

Case Report, 77-6564

Environmental Hazard**Polychlorobiphenyl Compounds**

Carcinogenic Potential, Review, 77-6015

Toxicity, Review, 77-6015

Epoxide Hydratases**Benzene, (Epoxyethyl)-**

Metabolism, 77-6158

Benzo(a)pyrene 4,5-Oxide

Metabolism, 77-6061

Drugs

Metabolism, 77-6061

Ergocalciferol**Virus, Murine Mammary Tumor**

Cell Transformation, Neoplastic, 77-6242

Dose-Response Study, 77-6242

Erythrocytes**Lymphoid Tissue**

Rosette Formation, Chick, 77-6472

Lymphoma, Lymphocytic

Lymphocytes, 77-6471

Mycobacterium bovis

Endocytosis, 77-6462

Toxoplasma gondii

Endocytosis, 77-6462

Erythroleukemia**Virus, Friend Murine Leukemia**

Antigens, Viral, 77-6356

Cell Differentiation, 77-6355

Immune Serums, 77-6356

Statolon, 77-6356

Escherichia coli**Urea, Methyl Nitroso-**

DNA, 77-6278

Esophageal Neoplasms**Carcinoma**

Diethylamine, *N*-Nitroso-, 77-6252

Carcinoma, Epidermoid

Ultrastructural Study, Monkey, 77-6508

Virus-Like Particles, 77-6508

Diet

Epidemiology, 77-6569

Diethylamine, *N*-Nitroso-

Histological Study, Rat, 77-6252

Precancerous Conditions, 77-6252

Smoking

Epidemiology, 77-6123

Estr-4-en-3-one, 7 α ,17-Dimethyl-17 β -Hydroxy**Virus, Rous Sarcoma**

Antibody Formation, 77-6453

Bursa of Fabricius, 77-6453

Cell Transformation, Neoplastic, 77-6453

Hematopoietic Stem Cells, 77-6453

Immunity, Cellular, 77-6453

Estradiol**Abnormalities**

Vagina, Mouse, 77-6230

Breast

Epidemiology, 77-6233

Breast Neoplasms

Carcinoma, 77-6030

Epidemiology, 77-6118

Estrogens

Metabolism, 77-6030

Gynecologic Neoplasms

Adenocarcinoma, 77-6229

Precancerous Conditions, 77-6229

Strain Difference, Mouse, 77-6229

Mammary Neoplasms, Experimental

Neoplasm Transplantation, 77-6203

Precancerous Conditions, 77-6229

Strain Difference, Mouse, 77-6229

Ultrastructural Study, Mouse, 77-6229

Retinol Acetate

Vagina, Mouse, 77-6230

Uterine Neoplasms

Carcinoma, 77-6030

Estradiol, 17-Ethynyl-**Liver**

Carcinogenic Metabolite, 77-6035

- Estradiol, 17-Ethynyl-** (cont'd)
Metabolism, 77-6035
- Estragol**
see Anisole, *p*-Allyl-
- Estriol**
Breast Neoplasms
Epidemiology, 77-6118
- Estrogens**
Carcinogenic Potential
Review, 77-6034
Estradiol
Metabolism, 77-6030
Estrone
Metabolism, 77-6030
Mammary Neoplasms, Experimental
Animal Model, Mouse, 77-6232
Dietary Fats, 77-6234
Progesterone, 77-6235
Metabolism
Review, 77-6037
Ovarian Neoplasms
Epidemiology, 77-6231
Uterine Neoplasms
Carcinoma, 77-6032, 77-6033
Epidemiology, 77-6031
Review, 77-6034
- Estrogens, Conjugated**
Breast Neoplasms
Review, 77-6034
- Estrone**
Breast
Epidemiology, 77-6233
Breast Neoplasms
Epidemiology, 77-6118
Estrogens
Metabolism, 77-6030
Mammary Neoplasms, Experimental
Histological Study, 77-6528
- Ethane, 1,2-Bis(chloromethoxy)-**
Carcinoma, Epidermoid
Mouse, 77-6047
Sarcoma
Mouse, 77-6047
Skin Neoplasms
Papilloma, 77-6047
- Ethane, 1,2-Dibromo-**
Carcinogenic Potential
Mouse, 77-6041
Rat, 77-6041
Salmonella typhimurium
Mutagenic Activity, 77-6041
Stomach Neoplasms
Carcinoma, Epidermoid, 77-6041
- Ethane, Tetrachloro-**
Water Pollution
Review, 77-6025
- Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-**
Water Pollution
Review, 77-6025
- Ethanol, 2,2'-(Phenylamino)di-, *N*-Nitroso-**
Tobacco
Concentration Levels, 77-6184
- Ethenamine, *N*-Ethylene-*N*-nitroso-**
Pancreatic Neoplasms
Carcinogenic Potential, Hamster, 77-6248
Respiratory Tract Neoplasms
Adenocarcinoma, 77-6248
Carcinoma, Epidermoid, 77-6248
Neoplasm Metastasis, 77-6248
- Ether, Bis(pentabromophenyl)-**
Toxicology
Review, 77-6151
- Ether, Bis(2-chloro-1-methylethyl)-**
Water Pollutants
Metabolism, Monkey, Rat, 77-6154
- Ether, Chloromethyl Methyl**
Lung Neoplasms
Epidemiology, 77-6071
Occupational Hazard, 77-6071
Smoking, 77-6071
Smoking
Co-carcinogenic Effect, 77-6071
- Ethionine**
see Butyric Acid, 2-Amino-4-(ethylthio)-
- Ethyl Alcohol**
Aryl Hydrocarbon Hydroxylases
DNA, 77-6182
Benzo(a)pyrene
Metabolism, 77-6182
Chromosomes
Mutagenic Activity, 77-6181
Lymphocytes
Chromosome Aberrations, 77-6181
- Ethylene, Chloro-**
Cell Transformation, Neoplastic
Dose-Response Study, 77-6013
Liver Neoplasms
Angiosarcoma, 77-6113
Metabolism
Review, 77-6039
Microsomes, Liver
Metabolism, 77-6157
Nucleic Acids, 77-6157
Poly A
Nucleic Acids, 77-6157
Ribonucleotides
Nucleic Acids, 77-6157
Salmonella typhimurium
Mutagenic Activity, 77-6039
- Ethylene, 1,1-Dichloro-**
Metabolism
Review, 77-6039
Salmonella typhimurium
Mutagenic Activity, 77-6039
- Ethylene, Trichloro-**
Metabolism
Review, 77-6039
Salmonella typhimurium
Mutagenic Activity, 77-6039
- Ethylenethiourea**
see 2-Imidazolidinethione
- Eugenol**
see Phenol, 2-Methoxy-4-(2-propenyl)-

- Exonucleases**
DNA Repair
Enzymatic Activity, 77-6130
- Fatty Acids**
Dimethylamine, *N*-Nitroso-
Metabolism, 77-6259
- Fetal Globulins**
Neoplasms
Immunosuppression, 77-6099
- Fibroadenoma**
see Adenofibroma
- Fibroblasts**
Caffeine
Chromosome Aberrations, 77-6291
Cell Division
Plasminogen Activators, 77-6596
Cell Transformation, Neoplastic
Cell Migration Inhibition, 77-6598
Plasminogen Activators, 77-6596
Cells, Cultured
Plasminogen Activators, 77-6596
Cycloheximide
Chromosome Aberrations, 77-6291
Peptide Hydrolases
Plasminogen Activators, 77-6596
Plasminogen Activators
Culture Media, 77-6596
Proteins
Degradation, Intracellular, 77-6588
- Fibroma**
Ovarian Neoplasms
Histological Study, Fish, 77-6526
- Fibrosarcoma**
Acetic Acid, Ester with 2,6-Dimethyl-*m*-dioxan-4-ol
Rat, 77-6048
Age Factors
Cell Survival, 77-6599
Lymphatic Metastasis, 77-6599
Antigens, Heterogenetic
Hypersensitivity, Delayed, 77-6444
BCG
Immunity, Cellular, 77-6461
Benz(a)anthracene, 7,12-Dimethyl-
BCG, 77-6461
Corynebacterium parvum, 77-6461
Transplantation Immunology, 77-6444
p-Benzoquinone
Rat, 77-6049
Cadmium
Rat, 77-6220
Cholanthrene, 3-Methyl-
Lymphatic Metastasis, 77-6599
Peptidoglycan, 77-6459
Uridine, 5-Bromo-2'-deoxy-, 77-6153
Uridine, 2'-Deoxy-5-iodo-, 77-6153
Corynebacterium parvum
Immunity, Cellular, 77-6461
Transplantation Immunology, 77-6444
Fluorescein, 2',4',5',7'-Tetrabromo-, Disodium Salt
Mammary Neoplasms, Experimental, 77-6055
Foreign Body Reaction
Cells, Cultured, 77-6497
Hypersensitivity, Delayed
Transplantation Immunology, 77-6444
- Fibrosarcoma (cont'd)**
T-Lymphocytes
Transplantation Immunology, 77-6444
Macrophages
Immunity, Cellular, 77-6461
Monocytes
Transplantation Immunology, 77-6444
Mycobacterium bovis
Transplantation Immunology, 77-6444
Neoplasm Transplantation
Immunity, 77-6454
Peptidoglycan
Immunity, Cellular, 77-6459
Radiation, Ionizing
Transplantation Immunology, 77-6444
Silica
Transplantation Immunology, 77-6444
Trypan Blue
Transplantation Immunology, 77-6444
Virus, Herpes Simplex 2
Hamster, 77-6088
- Fibroblastoma, Malignant**
see Fibrosarcoma
- Flavone**
Mutagenic Activity
Enzyme Activation, 77-6179
- Fluorescein, 2',4',5',7'-Tetrabromo-, Disodium Salt**
Liver Neoplasms
Sarcoma, 77-6055
Mammary Neoplasms, Experimental
Adenofibroma, 77-6055
Fibrosarcoma, 77-6055
- Food Contamination**
Carcinogen, Environmental
Diethylamine, *N*-Nitroso-, 77-6065
Dimethylamine, *N*-Nitroso-, 77-6065
Pyrrolidine, 1-Nitroso-, 77-6065
- Foreign Body Reaction**
Cells, Cultured
Histological Study, 77-6497
Fibrosarcoma
Cells, Cultured, 77-6497
- Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-**
Bladder Neoplasms
Carcinoma, Epidermoid, 77-6003
Carcinoma, Transitional Cell, 77-6003
Excretion, Dog, 77-6138
Histological Study, 77-6139
Tryptophan, 77-6139
Urine
Mutagenic Activity, 77-6138
- Formic Acid, 1-Methyl Hydrazide**
Gastrointestinal Neoplasms
Carcinogenic Potential, Mouse, 77-6172
Lung Neoplasms
Carcinogenic Potential, Mouse, 77-6172
- 2-Formylamine-4-(5-nitro-2-furyl)-thiazol**
see Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
- Galactosyltransferases**
Mammary Neoplasms, Experimental
Cell Membrane, 77-6480
Neoplasm Metastasis, 77-6480

- Gamma Globulins**
Virus, Herpes Simplex 1
Antibody Formation, 77-6486
- Gastric Mucosa**
Hyperplasia
Polychlorobiphenyl Compounds, 77-6149
- Gastrointestinal Neoplasms**
Carcinoma
Asbestos, 77-6073
Diet
Cholesterol, 77-6122
Dimethylamine, *N*-Nitroso-
Carcinogenic Activity, 77-6069
Formic Acid, 1-Methyl Hydrazide
Carcinogenic Potential, Mouse, 77-6172
Genetics
Epidemiology, 77-6571
Urea, Ethyl Nitroso-
Carcinogenic Activity, 77-6069
- Gastrointestinal System**
Arsenic
Toxicity, Review, 77-6014
Plutonium
Dose-Response Study, 77-6075
- Geldanamycin**
Cholanthrene, 3-Methyl-
Cell Transformation, Neoplastic, 77-6197
Virus, Murine Leukemia
Cells, Cultured, 77-6197
- Genetics**
Breast Neoplasms
Epidemiology, 77-6571
Epidemiology, Review, 77-6115
Carcinogen, Environmental
Cell Transformation, Neoplastic, 77-6101
Immune Response, Review, 77-6102
Chloroform
Toxicology, 77-6155
Colonic Neoplasms
Neoplasms, Multiple Primary, 77-6506
Polyps, 77-6506
Cytochrome P-450
Metabolism, 77-6018
Gastrointestinal Neoplasms
Epidemiology, 77-6571
Gynecologic Neoplasms
Epidemiology, 77-6571
Leukemia
Epidemiology, Cattle, 77-6559
Marek's Disease
Histocompatibility Antigens, 77-6327
Nasopharyngeal Neoplasms
Case Report, 77-6512
Parathyroid Neoplasms
Carcinoma, 77-6539
Case Report, 77-6539
Hyperparathyroidism, 77-6539
Respiratory Tract Neoplasms
Epidemiology, 77-6571
Retinoblastoma
Neoplasms, Multiple Primary, 77-6551
Skin Neoplasms
Epidemiology, 77-6571
Urogenital Neoplasms
Neoplasms, Multiple Primary, 77-6551
- Genetics (cont'd)**
Viral Proteins
Models, Theoretical, 77-6108
Virus, C-Type RNA Tumor
Cells, Cultured, 77-6343
Models, Theoretical, 77-6108
Virus, Marek's Disease Herpes
Chicken, 77-6328, 77-6482
Virus, SV40
DNA, Viral, 77-6433
- Glucosamine**
Virus, Rous Sarcoma
Peptides, 77-6307
- Glucose, 2-Deoxy-**
Virus, Rous Sarcoma
Peptides, 77-6307
- Glucosephosphatase**
Diethylamine, *N*-Nitroso-
Cell Transformation, Neoplastic, 77-6253
Liver, Rat, 77-6253
Hepatoma
Cytochemical Study, 77-6515
- Glucosephosphate**
Diethylamine, *N*-Nitroso-
Liver, Rat, 77-6251
- Glucosephosphate Dehydrogenase**
Carcinoma, Transitional Cell
Cells, Cultured, 77-6534
Corticotropin, 77-6534
- Glycinonitrile**
Dimethylamine, *N*-Nitroso-
DNA, Liver, 77-6254
- Glycoproteins**
Benzyl Alcohol, 3,4-Dihydroxy-
2-((isopropylamino)methyl)-
Trachea, 77-6070
Cell Transformation, Neoplastic
Isolation and Characterization, 77-6129
Mammary Neoplasms, Experimental
Antigen Shedding, 77-6480
Neoplasm Metastasis, 77-6480
Melanoma
Antigen Shedding, 77-6589
Cell Membrane, 77-6589
Cells, Cultured, 77-6589
Isolation and Characterization, 77-6589
Trypsin, 77-6589
Smoking
Trachea, 77-6070
- Goiter**
Thyroid Neoplasms
Neoplasms, Multiple Primary, 77-6543
- Gold**
Carcinogenic Activity
Rat, 77-6220
- Gonadoblastoma**
see Disgerminoma
- Graft vs Host Reaction**
Immunosuppression
Antibody Formation, 77-6449
T-Lymphocytes
Histocompatibility Antigens, 77-6449

Graft vs Host Reaction (cont'd)
Immunosuppression, 77-6449

Granular Cell Tumor, Malignant
see Sarcoma

Granuloma
Carrageen
Hydrolases, 77-6289
Muramidase, 77-6289
Phagocytes, 77-6289
Lymphocytes
Immune Response, 77-6470

Granulosa Cell Tumor
Ovarian Neoplasms
Histological Study, Fish, 77-6526

Growth Substances
Mammary Neoplasms, Experimental
Tissue Extracts, Liver, Fetus, 77-6457
Virus, Epstein-Barr
Genome-Negative Lymphoblastoid Cell Line
77-6408
Virus Replication, 77-6408

Guanidine, Dodecyl-, Acetate
Hepatoma
Mouse, 77-6274
Nitrous Acid, Sodium Salt, 77-6274
Lung Neoplasms
Adenoma, 77-6274
Mouse, 77-6274
Lymphoma
Mouse, 77-6274
Nitrous Acid, Sodium Salt, 77-6274

Guanidine, Methyl-
Hepatoma
Mouse, 77-6274
Nitrous Acid, Sodium Salt, 77-6274
Lung Neoplasms
Adenoma, 77-6274
Mouse, 77-6274
Lymphoma
Mouse, 77-6274
Nitrous Acid, Sodium Salt, 77-6274

Guanidine, 1-Methyl-3-nitro-1-nitroso-
Chromosome Aberrations
Embryo, Hamster, 77-6272
G-Banding, 77-6272
Xeroderma Pigmentosum, 77-6287
DNA
Mutagenic Activity, 77-6067
DNA Repair
Cells, Cultured, 77-6005
Xeroderma Pigmentosum, 77-6287
Guanosine Cyclic 3',5' Monophosphate
Colon, Liver, Rat, 77-6273
Guanyl Cyclase
Colon, Liver, Rat, 77-6273
Phenol, (1,1-Dimethylethyl)-4-methoxy-
Guanyl Cyclase, 77-6273
Retinol
Guanyl Cyclase, 77-6273
Stomach Neoplasms
Carcinoma, 77-6271
Precancerous Conditions, 77-6271
Ultrastructural Study, Rat, 77-6271

Guanosine
Methane, Diazo-
Methylation Products, 77-6275

Guanosine Cyclic 3',5' Monophosphate
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Colon, Liver, Rat, 77-6273

Guanyl Cyclase
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Colon, Liver, Rat, 77-6273
Phenol, (1,1-Dimethylethyl)-4-methoxy-, 77-6273
Retinol, 77-6273
Hydrazine
Colon, Liver, Rat, 77-6273
Quinoline, 4-Nitro-, 1-Oxide
Colon, Liver, Rat, 77-6273
Urea, Methyl Nitroso-
Colon, Liver, Rat, 77-6273

Gynecologic Neoplasms
Adenocarcinoma
Estradiol, 77-6229
4,4'-Stilbenediol, α,α' -Diethyl-, 77-6229
Carcinoma
Cell Cycle Kinetics, 77-6576
Estradiol
Precancerous Conditions, 77-6229
Strain Difference, Mouse, 77-6229
Genetics
Epidemiology, 77-6571
Neoplasm Metastasis
Cell Cycle Kinetics, 77-6576
4,4'-Stilbenediol, α,α' -Diethyl-
Strain Difference, Mouse, 77-6229
Testosterone, Propionate
Dose-Response Study, 77-6245
Histological Study, Mouse, 77-6245
Precancerous Conditions, 77-6245
Transplacental Carcinogenesis, Mouse, 77-6245

Head and Neck Neoplasms
Acetic Acid, Ester with 2,6-Dimethyl-*m*-dioxan-4-ol
Carcinoma, Epidermoid, 77-6048
Hodgkin's Disease
Neoplasm Metastasis, 77-6549
Radiation, Ionizing
Review, 77-6080
Sarcoma
Neoplasm Metastasis, 77-6549

Heavy Chain Disease
Immunoglobulins, Heavy Chain
Histological Study, 77-6474
Lymphoma
Histological Study, 77-6474

HeLa Cells
Virus, Adeno 2
Cell-Cycle Kinetics, 77-6391
Virus Replication, 77-6391

Hemangioma
Acetic Acid, 2,4-Dichlorophenoxy-
Rat, 77-6052
Liver Neoplasms
Resorcinol, 77-6042
Succinic Acid, Mono(2,2-dimethylhydrazide)
Mouse, 77-6168

- Hemangiopericytoma**
Brain Neoplasms
Ultrastructural Study, 77-6547
- Hemangiosarcoma**
see Angiosarcoma
- Hematopoietic Stem Cells**
Cell Differentiation
Chick Embryo, 77-6452
Immunosuppression, 77-6452
Leukemia, Myeloblastic
Cells, Cultured, 77-6591
Transplantation, Homologous
Chick Embryo, 77-6452
Virus, Rous Sarcoma
Estr-4-en-3-one, 7 α ,17-Dimethyl-17 β -Hydroxy
77-6453
- Heme**
Carcinogen, Chemical
Carrier Proteins, 77-6142
- Hemoglobins**
Mycobacterium bovis
Endocytosis, 77-6462
Smoking
Dose-Response Study, Mouse, 77-6191
Toxoplasma gondii
Endocytosis, 77-6462
Virus, Friend Murine Leukemia
Cell Differentiation, 77-6355
- Hepatoma**
Acetamide, *N*-Fluoren-2-yl-
Mouse, 77-6135
Transplacental Carcinogenesis, 77-6135
Acetic Acid, Ester with 2,6-Dimethyl-*m*-dioxan-4-ol
Rat, 77-6048
Acetic Acid, 2,4,5-Trichlorophenoxy-
Mouse, 77-6051
Aflatoxin B1
Corticotropin, 77-6174
Insulin, 77-6174
Somatotropin, 77-6174
Androgens
Histological Study, 77-6246
Aniline, *N,N*-Dimethyl-*p*-phenylazo-
Radiation, Ionizing, 77-6456
Antigens, Neoplasm
Transplantation Immunology, 77-6456
Australia Antigen
Antigen Frequency, 77-6388
Diethylamine, *N*-Nitroso-
Histological Study, Fish, 77-6249
Temperature, 77-6249
Glucosephosphatase
Cytochemical Study, 77-6515
Guanidine, Dodecyl-, Acetate
Mouse, 77-6274
Nitrous Acid, Sodium Salt, 77-6274
Guanidine, Methyl-
Mouse, 77-6274
Nitrous Acid, Sodium Salt, 77-6274
Liver Cirrhosis
Australia Antigen, 77-6388
Liver Neoplasms
Epidemiology, 77-6237
Neoplasms, Multiple Primary
Androsta-1,4-dien-3-one, 17-Hydroxy-17-methyl-
77-6244
Pancreatic Neoplasms
Androgens, 77-6246
Prednisone
Case Report, 77-6246
Propanol, 1,1'-Iminodi-*N*-nitroso-
Histological Study, Guinea Pig, 77-6265
Pyruvate Kinase
Case Report, Minimal Deviation Tumor, 77-6514
Isoenzymes, 77-6514
Radiation, Ionizing
Transplantation Immunology, 77-6456
Testosterone
Case Report, 77-6246
Virus, Hepatitis B
Epidemiology, 77-6388
- Hepatoma (cont'd)**
Androsta-1,4-dien-3-one, 17-Hydroxy-17-methyl-
77-6244
Pancreatic Neoplasms
Androgens, 77-6246
Prednisone
Case Report, 77-6246
Propanol, 1,1'-Iminodi-*N*-nitroso-
Histological Study, Guinea Pig, 77-6265
Pyruvate Kinase
Case Report, Minimal Deviation Tumor, 77-6514
Isoenzymes, 77-6514
Radiation, Ionizing
Transplantation Immunology, 77-6456
Testosterone
Case Report, 77-6246
Virus, Hepatitis B
Epidemiology, 77-6388
- Hereditary Diseases**
Carcinogen, Environmental
Cell Transformation, Neoplastic, 77-6101
Neoplasms, Multiple Primary
Cell Transformation, Neoplastic, 77-6101
- Hexoses**
Virus, Murine Sarcoma
Cell Transformation, Neoplastic, 77-6368
- Histocompatibility Antigens**
Autoimmune Diseases
Immune Response, Review, 77-6096
Cell Transformation, Neoplastic
Antigenic Determinants, Review, 77-6095
Cervix Neoplasms
Carcinoma, 77-6487
Epidemiology, 77-6487
Cholanthrene, 3-Methyl-
Transplantation Immunology, 77-6448, 77-6493
Graft vs Host Reaction
T-Lymphocytes, 77-6449
Guinea Pig
Review, 77-6093
Hodgkin's Disease
Epidemiology, Review, 77-6094
Immune Response, Review, 77-6095
Intestinal Neoplasms
Epidemiology, Review, 77-6094
Leukemia
Immune Response, Review, 77-6095
Leukemia, Lymphoblastic
Epidemiology, Review, 77-6094
Immune Response, Review, 77-6094
Leukemia, Lymphocytic
Immune Response, Review, 77-6096
Lymphoma
Tumor Dormancy, 77-6455
Marek's Disease
Chicken, 77-6327
Genetics, 77-6327
Nasopharyngeal Neoplasms
Epidemiology, Review, 77-6094
Immune Response, Review, 77-6096
Neoplasms
Epidemiology, 77-6099
Plasmacytoma
IgA, 77-6479

Histocompatibility Antigens (cont'd)

- Sarcoma
 - Transplantation Immunology, 77-6493
- Virus, Adeno 3
 - Immune Response, 77-6334
- Virus, Avian Leukosis
 - Antibody Formation, 77-6467
 - B-Lymphocytes, 77-6467
- Virus, Marek's Disease Herpes
 - Chicken, 77-6482
- Virus, Moloney Murine Sarcoma
 - Macrophages, 77-6486
 - Migration Inhibitory Factor, 77-6486
- Virus, Radiation Leukemia
 - Immune Response, 77-6346
- Virus, SV40
 - Cell Membrane, 77-6427
 - Cell Nucleus, 77-6427
 - Cell Transformation, Neoplastic, 77-6427
 - Transplantation Immunology, 77-6427

Histones

- RNA, Messenger
 - Isolation and Characterization, 77-6594
- Virus, SV40
 - Metabolism, 77-6423

Hodgkin's Disease

- Antigens
 - Cells, Cultured, 77-6488
 - Isolation and Characterization, 77-6488
- Antigens, Neoplasm
 - Isolation and Characterization, 77-6489
- Cell Membrane
 - Surface Properties, 77-6565
- Colonic Neoplasms
 - Enteritis, Regional, 77-6564
- Enteritis, Regional
 - Case Report, 77-6564
- Epidemiology
 - Review, 77-6125
- Head and Neck Neoplasms
 - Neoplasm Metastasis, 77-6549
- Histocompatibility Antigens
 - Epidemiology, Review, 77-6094
 - Immune Response, Review, 77-6095
- Horizontal Transmission
 - Epidemiology, 77-6570
- Leukemia, Lymphoblastic
 - 77-6506
- Lymphocytes
 - DNA Replication, 77-6473
- B-Lymphocytes
 - Surface Properties, 77-6565

Hormones

- Breast Neoplasms
 - Epidemiology, 77-6116

Hyaluronidase

- Lymphoid Tissue
 - Rosette Formation, Chick, 77-6472

Hydantoin, 5,5-Diphenyl-

- Leukemia, Myeloblastic
 - Review, 77-6060
- Lymphoma
 - Review, 77-6060

Hydantoin, 5,5-Diphenyl- (cont'd)

- Neuroblastoma
 - Review, 77-6060

Hydrazine

- Guanyl Cyclase
 - Colon, Liver, Rat, 77-6273

Hydrazine, 1,1-Dimethyl-

- Colonic Neoplasms
 - Adenocarcinoma, 77-6171
 - Cell Division, 77-6171
 - Resection, Small Intestine, 77-6170
 - Surgery, Operative, 77-6170
- 3,6-Pyridazinedione, 1,2-Dihydro-
 - Tobacco, 77-6184
- Tobacco
 - Concentration Levels, 77-6184

Hydrazine, 1,2-Dimethyl-

- Cells, Cultured
 - Metabolism, 77-6298
- Colonic Neoplasms
 - Ultrastructural Study, Rat, 77-6566
- Intestinal Neoplasms
 - Bile Acids and Salts, 77-6169
 - Diet, 77-6169
 - Dietary Fats, 77-6121

Hydro-Lyases

- Benzo(a)pyrene
 - Propane, 1,2-Epoxy-3,3,3-trichloro-, 77-6213
- Benzo(a)pyrene 4,5-Oxide
 - Spectrofluorimetric Assay, 77-6207

Hydrolases

- Granuloma
 - Carrageen, 77-6289

Hydroquinone

- Bladder Neoplasms
 - Carcinoma, 77-6042

Hydroxyindoleacetic Acid

- Prostatic Neoplasms
 - Carcinoma, Epidermoid, 77-6247

Hydroxylamine, N-4-Biphenyl-

- 4-Biphenylamine
 - Carcinogenic Metabolite, 77-6147

Hydroxylamine, N-1-Naphthyl-

- Skin Neoplasms
 - Rat, 77-6286

Hydroxylamine, N-2-Naphthyl-

- Liver Neoplasms
 - Rat, 77-6286
- Lymphosarcoma
 - Rat, 77-6286

Hydroxylases

- Ellipticine
 - Microsomes, Liver, 77-6206

Hypercalcemia

- Sarcoma, Osteogenic
 - Virus, Moloney Murine Sarcoma, 77-6365

Hypercholesterolemia

- 2-Imidazolidinethione
 - Dose-Response Study, 77-6283

- Hyperparathyroidism**
Parathyroid Neoplasms
Genetics, 77-6539
- Hyperplasia**
Breast Neoplasms
Precancerous Conditions, 77-6111
Gastric Mucosa
Polychlorobiphenyl Compounds, 77-6149
Laryngeal Neoplasms
Smoking, 77-6188
Ultrastructural Study, Rat, 77-6188
Mammary Neoplasms, Experimental
DU 41274, 77-6239
Stomach Neoplasms
Polychlorobiphenyl Compounds, 77-6149
- Hypersensitivity, Delayed**
Fibrosarcoma
Antigens, Heterogenetic, 77-6444
Transplantation Immunology, 77-6444
- Hypoxanthine**
Virus, Friend Murine Leukemia
Cell Differentiation, 77-6355
- Hypoxanthine Phosphoribosyltransferase**
Cell Transformation, Neoplastic
Nucleotides, 77-6595
Virus, SV40
Cell Transformation, Neoplastic, 77-6595
- IgA**
Plasmacytoma
Antigens, Neoplasm, 77-6479
Histocompatibility Antigens, 77-6479
- IgG**
Multiple Myeloma
Temperature Dependence, 77-6476
Virus, Herpes Simplex
Immunity, Cellular, 77-6435
B-Lymphocytes, 77-6435
T-Lymphocytes, 77-6435
Virus, Herpes Simplex 1
Antibody Formation, 77-6486
- Imidazole-4-carboxamide, 5-(3,3-Dimethyl-1-triazeno)-**
Antineoplastic Agents
Carcinogenic Activity, Mouse, 77-6295
- 2-Imidazolidinethione**
Fetus
Metabolism, Mouse, Rat, 77-6282
Hypercholesteremia
Dose-Response Study, 77-6283
Liver
Enzymatic Activity, 77-6283
Histological Study, Hamster, Rat, 77-6283
Pregnancy
Half-Life, Blood, 77-6282
Metabolism, Mouse, Rat, 77-6282
Thyroid Gland
Histological Study, Hamster, Rat, 77-6283
Thyroid Neoplasms
Rat, 77-6283
Urine
Metabolites, 77-6282
- Immune Serums**
Erythroleukemia
Virus, Friend Murine Leukemia, 77-6356
- Immune Serums (cont'd)**
Lymphoma
Transplantation Immunology, 77-6458
Virus, C-Type RNA Tumor
Antigen-Antibody Reactions, 77-6495
Lipopolysaccharides, 77-6495
- Immunity**
Fibrosarcoma
Neoplasm Transplantation, 77-6454
- Immunity, Cellular**
Bacillus megaterium, 77-6459
BCG
Carrageen, 77-6461
Silica, Crystalline, 77-6461
Cholanthrene, 3-Methyl-
Virus, Avian Sarcoma, 77-6481
Corynebacterium parvum
Carrageen, 77-6461
Silica, Crystalline, 77-6461
Fibrosarcoma
BCG, 77-6461
Corynebacterium parvum, 77-6461
Macrophages, 77-6461
Peptidoglycan, 77-6459
- Leukemia**
Cells, Cultured, 77-6434
Isotope Release Assay, 77-6434
Virus, Murine Leukemia, 77-6434
- T-Lymphocytes**
Antigens, Neoplasm, 77-6486
- Lymphoma**
Mouse, 77-6450
Macrophages, 77-6459
Neoplasms, Experimental
Isotope Release Assay, 77-6434
Virus, Adeno 7 - SV40 Hybrid, 77-6439
- Sarcoma**
Neoplasm Metastasis, 77-6451
- Smoking**
Macrophages, 77-6192
Virus, Adeno 7 - SV40 Hybrid
Antigen-Antibody Reactions, 77-6439
- Virus, Avian Leukosis**
Antigenic Determinants, 77-6481
- Virus, Avian Sarcoma**
Antigenic Determinants, 77-6481
- Virus, Herpes Simplex**
IgG, 77-6435
Immunoglobulins, Fc, 77-6435
Killer Cells, 77-6435
T-Lymphocytes, 77-6435
Virus, Herpes Simplex 1
Antigen-Antibody Reactions, 77-6486
Virus, Marek's Disease Herpes
Viral Vaccines, 77-6483
Virus, Turkey Herpes, 77-6483
Virus, Rous Sarcoma
Estr-4-en-3-one, 7 α ,17-Dimethyl-17 β -Hydroxy
77-6453
- Immunoglobulins**
Inulin
Binding, 77-6475
B-Lymphocytes
Chick Embryo, 77-6452
Plasmacytoma
Isolation and Characterization, 77-6475

- Immunoglobulins, Fc**
 - Lymphoma
 - Lymphocytes, 77-6471
 - Lymphoma, Lymphocytic
 - Lymphocytes, 77-6471
 - Multiple Myeloma
 - Temperature Dependence, 77-6476
 - Virus, Herpes Simplex
 - Immunity, Cellular, 77-6435
 - Virus, Herpes Simplex 1
 - Antibody Formation, 77-6486
- Immunoglobulins, Heavy Chain**
 - Heavy Chain Disease
 - Histological Study, 77-6474
- Immunoglobulins, Light Chain**
 - Multiple Myeloma
 - Temperature Dependence, 77-6476
- Immunoglobulins, Surface**
 - B-Lymphocytes
 - Leukemia, 77-6477
 - Lymphoma
 - Lymphocytes, 77-6471
 - Lymphoma, Lymphocytic
 - Lymphocytes, 77-6471
- Immunologic Deficiency Syndromes**
 - Leukemia
 - Precancerous Conditions, Review, 77-6105
 - Neoplasms
 - Review, 77-6099
 - Virus, Epstein-Barr
 - Case Report, 77-6557
- Immunosuppression**
 - Bronchial Neoplasms
 - Histological Study, Dog, 77-6215
 - Cholanthrene, 3-Methyl-
 - Strain Difference, Mouse, 77-6196
 - Graft vs Host Reaction
 - Antibody Formation, 77-6449
 - T-Lymphocytes, 77-6449
 - Hematopoietic Stem Cells
 - Cell Differentiation, 77-6452
 - B-Lymphocytes
 - Cell Differentiation, 77-6452
 - Neoplasms
 - Carcinoembryonic Antigen, 77-6099
 - Fetal Globulins, 77-6099
 - Neoplasms, Experimental
 - T-Lymphocytes, 77-6447, 77-6448
 - Virus, C-Type RNA Tumor
 - Antigen-Antibody Reactions, 77-6495
- Infectious Mononucleosis**
 - Cell Membrane
 - Surface Properties, 77-6565
 - B-Lymphocytes
 - Surface Properties, 77-6565
 - Virus, Epstein-Barr
 - Antigens, Viral, 77-6409
- Insulin**
 - Hepatoma
 - Aflatoxin B1, 77-6174
 - Mammary Neoplasms, Experimental
 - Neoplasm Transplantation, 77-6203
- Interferon**
 - Virus, Kirsten Murine Sarcoma
 - Reverse Transcriptase, 77-6370
 - Virus, Moloney Murine Leukemia
 - Viral Proteins, 77-6363
 - Virus Replication, 77-6361
 - Virus, Murine Mammary Tumor
 - Antigens, Viral, 77-6375
 - Cells, Cultured, 77-6375
 - Reverse Transcriptase, 77-6375
 - Virus, SV40
 - Viral Proteins, 77-6422
 - Virus Replication, 77-6422
- Intestinal Neoplasms**
 - Adenocarcinoma
 - Neoplasms, Multiple Primary, 77-6550
 - Bracken Fern
 - Heat Treatment, 77-6177
 - Histological Study, 77-6177
 - Diet
 - Epidemiology, 77-6569
 - Dietary Fats
 - Epidemiology, Review, 77-6121
 - Histocompatibility Antigens
 - Epidemiology, Review, 77-6094
 - Hydrazine, 1,2-Dimethyl-
 - Bile Acids and Salts, 77-6169
 - Diet, 77-6169
 - Dietary Fats, 77-6121
 - Neoplasms, Multiple Primary
 - Case Report, 77-6550
- Inulin**
 - Immunoglobulins
 - Binding, 77-6475
- Iodine Radioisotopes**
 - Thyroid Neoplasms
 - Thyroxine, 77-6226
 - Uracil, 6-Propyl-2-thio-, 77-6226
- Isoenzymes**
 - Hepatoma
 - Pyruvate Kinase, 77-6514
- Isopropyl Alcohol**
 - Carcinogenic Potential
 - Mouse, 77-6054
 - Laryngeal Neoplasms
 - Epidemiology, 77-6054
 - Lung Neoplasms
 - Epidemiology, 77-6054
 - Respiratory Tract Neoplasms
 - Epidemiology, 77-6054
- Karyotyping**
 - Chromosomes
 - Cells, Cultured, 77-6516
- Kidney**
 - Cadmium Chloride
 - Body Burden, 77-6218
- Kidney Neoplasms**
 - Acetic Acid, Ester with 2,6-Dimethyl-*m*-dioxan-4-ol
 - Carcinoma, Transitional Cell, 77-6048
 - Adenocarcinoma
 - Virus, Lucke Herpes, 77-6567
 - Adenoma
 - Dimethylamine, *N*-Nitroso-, 77-6255

Kidney Neoplasms (cont'd)

Succinic Acid, Mono(2,2-dimethylhydrazide)
77-6168

Androgens

Case Report, 77-6246
Histological Study, 77-6246

Carcinoma

Dimethylamine, *N*-Nitroso-, 77-6255

Coal

Epidemiology, 77-6582

Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
Carcinogenic Potential, Rat, 77-6156

Dimethylamine, *N*-Nitroso-

Carcinogenic Activity, 77-6069
Orchiectomy, Mouse, 77-6255

Prednisone

Case Report, 77-6246

Succinic Acid, Mono(2,2-dimethylhydrazide)
Mouse, 77-6168

Testosterone

Case Report, 77-6246

Urea, Ethyl Nitroso-

Carcinogenic Activity, 77-6069

Virus, Lucke Herpes

Antigen-Antibody Reactions, 77-6567
Cell Aggregation, 77-6567
Ultrastructural Study, Ascites Cells, 77-6567

Lactation**Breast Neoplasms**

Epidemiology, 77-6117

Laryngeal Neoplasms**Carcinoma**

Asbestos, 77-6073

Hyperplasia

Smoking, 77-6188
Ultrastructural Study, Rat, 77-6188

Isopropyl Alcohol

Epidemiology, 77-6054

Metaplasia

Smoking, 77-6188
Ultrastructural Study, Rat, 77-6188

Smoking

Epidemiology, 77-6123
Mouse, 77-6243
Precancerous Conditions, 77-6188
Ultrastructural Study, Rat, 77-6188

Testosterone

Histological Study, 77-6243

Lead**Brain Neoplasms**

Astrocytoma, 77-6219
Case Report, 77-6219

RNA Polymerase

Carcinogenic Potential, 77-6217

Water Pollutants

Isolation and Characterization, 77-6585

Water Pollution

Review, 77-6025

Leukemia

Acetic Acid, Ester with 2,6-Dimethyl-*m*-dioxan-4-ol
Rat, 77-6048

Antigens, Neoplasm

Guinea Pig, 77-6092

Arsenic**Leukemia (cont'd)**

Toxicity, Review, 77-6014

Benzene

Epidemiology, Review, 77-6104

Cells, Cultured

Cytotoxicity Tests, Immunologic, 77-6437

Guinea Pig, 77-6090, 77-6091

Virus, Murine Leukemia, 77-6354

Chromosome Aberrations

Review, 77-6106

Chromosome Abnormalities

Precancerous Conditions, Review, 77-6105

Epidemiology, 77-6530

Review, 77-6125

Genetics

Epidemiology, Cattle, 77-6559

Histocompatibility Antigens

Immune Response, Review, 77-6095

Horizontal Transmission

Epidemiology, 77-6570

Immunity, Cellular

Cells, Cultured, 77-6434

Isotope Release Assay, 77-6434

Immunologic Deficiency Syndromes

Precancerous Conditions, Review, 77-6105

Lymphocytes

Cholesterol, 77-6592

DNA Replication, 77-6592

Plant Agglutinins, 77-6592

B-Lymphocytes

Immunoglobulins, Surface, 77-6477

Myeloproliferative Disorders

Precancerous Conditions, Review, 77-6105

Radiation

Occupational Hazard, Review, 77-6081

Radiation, Ionizing

Dose-Response Study, 77-6082

Epidemiology, 77-6079, 77-6083, 77-6125

Epidemiology, Review, 77-6104

Urea, Ethyl Nitroso-

Chromosomes, 77-6279

Cytochemical Study, 77-6279

DNA, 77-6279

Neoplasm Transplantation, 77-6279

Ultrastructural Study, 77-6279

Virus, C-Type RNA Tumor

Epidemiology, Review, 77-6104

Virus, Guinea Pig Herpes-Like

Ultrastructural Study, 77-6091

Virus, Guinea Pig RNA Tumor

Ultrastructural Study, 77-6091

Virus, Murine Leukemia

Immunity, Cellular, 77-6434

Virus, RNA Tumor

Mouse, 77-6341

Leukemia, Acute Granulocytic

see Leukemia, Myeloblastic

Leukemia, Lymphoblastic**Antigens**

B-Lymphocytes, 77-6103

T-Lymphocytes, 77-6103

Cell Membrane

Surface Properties, 77-6565

Drug Therapy, Combination

Case Report, 77-6506

Histocompatibility Antigens

- Leukemia, Lymphoblastic (cont'd)**
 Epidemiology, Review, 77-6094
 Immune Response, Review, 77-6094
 Hodgkin's Disease
 Drug Therapy, Combination, 77-6506
 T-Lymphocytes
 Surface Properties, 77-6565
 Virus, Herpes
 Isolation and Characterization, Guinea Pig, 77-6338
- Leukemia, Lymphocytic**
 Antigens
 B-Lymphocytes, 77-6103
 T-Lymphocytes, 77-6103
 Chromosome Abnormalities
 Chromosomes, Human, 1-3, 77-6558
 Chromosomes, Human, 6-12, 77-6558
 Histocompatibility Antigens
 Immune Response, Review, 77-6096
 Virus, Gross Murine Leukemia
 T-Lymphocytes, 77-6560
 Mouse, AKR, 77-6560
- Leukemia, Monoblastic**
 Benzene
 Occupational Hazard, 77-6145
- Leukemia, Myeloblastic**
 Benzene
 Occupational Hazard, 77-6145
 Bone Marrow Cells
 Cells, Cultured, 77-6561
 Cells, Cultured
 Chromosome Aberrations, 77-6562
 Hematopoietic Stem Cells, 77-6591
 Hydantoin, 5,5-Diphenyl-
 Review, 77-6060
- Leukemia, Myelocytic**
 Bone Marrow Cells
 Cells, Cultured, 77-6561
 Neoplasms
 Review, 77-6107
 Propanol, 1,1'-Iminodi-*N*-nitroso-
 Histological Study, Guinea Pig, 77-6265
 Virus, Epstein-Barr
 Virus-Like Particles, 77-6414
 Virus, Herpes
 Chromosome Aberrations, Orangutan, 77-6414
 Virus-Like Particles, 77-6414
- Leukemia, Myelomonocytic**
 see Leukemia, Myelocytic
- Leukocytes**
 Virus, Epstein-Barr
 Cell Transformation, Neoplastic, 77-6405
 Virus, Feline Leukemia
 Antigens, Viral, 77-6331
 Virus, Herpes Simplex
 Killer Cells, 77-6435
- Leydig Cell Tumor**
 Fish
 Histological Study, 77-6537
 Ultrastructural Study, 77-6537
- Ligases**
 Acetamide, Thio-
 Mitochondria, 77-6133
- Lip Neoplasms**
 Papilloma
 Aquatic Animals, Review, 77-6023
- Lipids**
 Anthracene
 Cell Membrane, 77-6210
 Benzo(a)pyrene
 Cell Membrane, 77-6210
 Breast
 Epidemiology, 77-6233
 Liver Neoplasms
 Microsomes, 77-6210
 Mitochondria, 77-6210
 Virus, Murine Sarcoma
 Cell Transformation, Neoplastic, 77-6368
- Lipopolysaccharides**
 Virus, C-Type RNA Tumor
 Immune Serums, 77-6495
- Liposarcoma**
Perodicticus potto
 Case Report, 77-6152
 Trace Elements, 77-6152
 Triglycerides, 77-6152
- Liver**
 Acetamide, *N*-Fluoren-2-yl-
 Ultrastructural Study, Rat, 77-6136
 Acetamide, Thio-
 Mitochondria, 77-6133
 Aflatoxin B1
 Metabolism, 77-6058
 Antipyrine
 Metabolism, 77-6180
 Barbituric Acid, 5-(1-Cyclohexen-1-yl)-1,5-dimethyl-
 Metabolism, 77-6180
 Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
 Ultrastructural Study, Rat, 77-6136
 Benzo(a)pyrene
 DNA, Binding, 77-6204
 Metabolism, 77-6180
 Metabolism, Rat, 77-6204
 7,8-Benzoflavone
 Metabolism, 77-6180
 Benzoxazole, 2-Amino-5-chloro-
 Metabolism, 77-6180
 Butyric Acid, 2-Amino-4-(ethylthio)-
 Metabolism, Rat, 77-6164
 Chromosomes
 Cells, Cultured, 77-6516
 Coumarin
 Metabolism, 77-6180
 Coumarin, 7-Ethoxy-
 Metabolism, 77-6180
 Estradiol, 17-Ethynyl-
 Carcinogenic Metabolite, 77-6035
 Metabolism, 77-6035
 2-Imidazolidinethione
 Enzymatic Activity, 77-6283
 Histological Study, Hamster, Rat, 77-6283
 Mestranol
 Carcinogenic Metabolite, 77-6035
 Metabolism, 77-6035
 Mitochondria
 Rat, 77-6133
 Naphthalenemethanol, α -((Isopropylamino)methyl)-
 Carcinogenic Potential, Mouse, 77-6241

Liver (cont'd)

- 2-Propanol, 1-(2-Allyloxyphenoxy)-3-(isopropylamino)-
Carcinogenic Potential, Mouse, 77-6241

Liver Cirrhosis**Hepatoma**

- Australia Antigen, 77-6388

Liver Neoplasms

- Acetamide, *N*-Fluoren-2-yl-
Histological Study, Mouse, 77-6241
Phorbol, 77-6135
- Acetic Acid, Ester with 2,6-Dimethyl-*m*-dioxan-4-ol
Rat, 77-6048
- Adenoma
Androsta-1,4-dien-3-one, 17-Hydroxy-17-methyl-
77-6244
Contraceptives, Oral, 77-6036, 77-6113, 77-6237
Epidemiology, 77-6237
- Androsta-1,4-dien-3-one, 17-Hydroxy-17-methyl-
Case Report, 77-6244
- Anemia, Aplastic
Case Report, 77-6513
- Angiosarcoma
Ethylene, Chloro-, 77-6113
Propanol, 1,1'-Iminodi-*N*-nitroso-, 77-6265
Urea, Methyl Nitroso-, 77-6277
- Australia Antigen
Epidemiology, 77-6387
- Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
Antigens, Neoplasm, 77-6494
- Carcinoma
Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-,
77-6494
Contraceptives, Oral, 77-6238
Diethylamine, *N*-Nitroso-, 77-6004
Mirex, 77-6050
Models, Biological, 77-6004
Mycotoxins, 77-6036
Virus, Hepatitis, 77-6387
- Cholangioma
2-Propanol, 1,1'-Iminodi-*N*-nitroso-, 77-6264
77-6265
Urea, Methyl Nitroso-, 77-6277
- Contraceptives, Oral
Case Report, 77-6238
Pregnancy, 77-6238
- Dibenzo-*p*-dioxin
Mouse, 77-6040
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
Carcinogenic Potential, Rat, 77-6156
Epidemiology, 77-6040
Mouse, 77-6040
- Diethylamine, *N*-Nitroso-
Barbituric Acid, 5-Ethyl-5-phenyl-, 77-6004
Dose-Response Study, 77-6250
Precancerous Conditions, 77-6251
Progesterone, 77-6236
- Dimethylamine, *N*-Nitroso-
Carcinogenic Activity, 77-6069
- Hemangioma
Resorcinol, 77-6042
- Hepatoma
Epidemiology, 77-6237
- Hydroxylamine, *N*-2-Naphthyl-
Rat, 77-6286
- Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)
Fish, 77-6143

Liver Neoplasms (cont'd)

- Histological Study, 77-6143
- Microsomes
Lipids, 77-6210
Phospholipids, 77-6210
- Mitochondria
Lipids, 77-6210
Phospholipids, 77-6210
- Neoplasm Metastasis
Case Report, 77-6507
- Neoplasms, Multiple Primary
Androsta-1,4-dien-3-one, 17-Hydroxy-17-methyl-
77-6244
- Oxymetholone
Histological Study, 77-6513
- Prednisone
Histological Study, 77-6513
- 2-Propanol, 1,1'-Iminodi-*N*-nitroso-
Carcinogenic Activity, Hamster, 77-6264
Histological Study, Guinea Pig, 77-6265
- Sarcoma
Fluorescein, 2',4',5',7'-Tetrabromo-, Disodium Salt
77-6055
- Testosterone
Histological Study, 77-6513
- Urea, Methyl Nitroso-
Histological Study, Guinea Pig, 77-6277

Liver Regeneration

- Dimethylamine, *N*-Nitroso-
DNA Replication, 77-6256
- RNA
Cytoplasm, 77-6593
DNA-RNA Hybridization, 77-6593
Polyribosomes, 77-6593

Lung

- Plutonium
Dose-Response Study, 77-6075
- Plutonium Oxide
Clearance, Translocation, 77-6224
Sodium Oxide, 77-6224

Lung Neoplasms

- Adenocarcinoma
Arsenic, 77-6222
Arsenic Trioxide, 77-6222
Succinic Acid, Mono(2,2-dimethylhydrazide)
77-6168
- Adenoma
Arsenic, 77-6222
Arsenic Trioxide, 77-6222
Carbamic Acid, Ethyl Ester, 77-6162, 77-6163
Cell-cycle Kinetics, 77-6163
Guanidine, Dodecyl-, Acetate, 77-6274
Guanidine, Methyl-, 77-6274
Naphthalene, 2-Nitroso-, 77-6286
Resorcinol, 77-6042
Smoking, 77-6189
Succinic Acid, Mono(2,2-dimethylhydrazide)
77-6168
Urea, Ethyl Nitroso-, 77-6280
- Air Pollution
Epidemiology, Review, 77-6127
- Antigens, Neoplasm
Transplacental Carcinogenesis, 77-6491
- Arsenic
Epidemiology, 77-6223
- Arsenic Trioxide

Lung Neoplasms (cont'd)

- Benzo(a)pyrene, 77-6222
- Asbestos
 - Case Report, 77-6074
 - Epidemiology, 77-6074, 77-6577, 77-6578
 - Mesothelioma, 77-6578
- p*-Benzoquinone
 - Adenocarcinoma, 77-6049
- Carbamic Acid, Ethyl Ester
 - p*-Cresol, 2,6-Di-*tert*-butyl-, 77-6162
- Carcinoma
 - Asbestos, 77-6073
- Carcinoma, Epidermoid
 - Benzo(a)pyrene, 77-6222
 - Cholanthrene, 3-Methyl-, 77-6195
- Chloroform
 - Epidemiology, 77-6584
- Cholanthrene, 3-Methyl-
 - Cells, Cultured, 77-6195
 - Precancerous Conditions, 77-6195
- Coal
 - Benzo(a)pyrene, 77-6582
 - Epidemiology, 77-6582
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 - Carcinogenic Potential, Rat, 77-6156
 - Dose-Response Study, 77-6156
- Ether, Chloromethyl Methyl-
 - Epidemiology, 77-6071
 - Occupational Hazard, 77-6071
 - Smoking, 77-6071
- Formic Acid, 1-Methyl Hydrazide
 - Carcinogenic Potential, Mouse, 77-6172
- Guanidine, Dodecyl-, Acetate
 - Mouse, 77-6274
- Guanidine, Methyl-
 - Mouse, 77-6274
- Isopropyl Alcohol
 - Epidemiology, 77-6054
- Isopropyl Oils
 - Mouse, 77-6054
- T-Lymphocytes
 - Immune Response, 77-6442
 - Transplantation Immunology, 77-6442
- Mesothelioma
 - Asbestos, 77-6577
- Neurilemmoma
 - Neoplasm Metastasis, 77-6544
 - Transplantation, Heterologous, 77-6544
- Occupational Hazard
 - Epidemiology, Review, 77-6127
- Papilloma
 - Smoking, 77-6189
- Phenylhydrazine, 4-Hydroxymethyl-
 - Carcinogenic Potential, Mouse, 77-6172
- Smoking
 - Diet, Review, 77-6127
 - Dose-Response Study, 77-6250
 - Epidemiology, 77-6123
 - Epidemiology, Review, 77-6124, 77-6127
 - Genetics, Review, 77-6127
 - Macrophages, 77-6189
 - Precancerous Conditions, 77-6189, 77-6510
 - Ultrastructural Study, Hamster, 77-6189
- Succinic Acid, Mono(2,2-dimethylhydrazide)
 - Mouse, 77-6168
- Transplantation, Heterologous
 - Precancerous Conditions, 77-6510

Lung Neoplasms (cont'd)

- Smoking, 77-6510
- Ultrastructural Study, 77-6510
- Urea, Ethyl Nitroso-
 - Transplacental Carcinogenesis, 77-6280, 77-6491

Lymphatic Metastasis

- Fibrosarcoma
 - Age Factors, 77-6599
 - Cholanthrene, 3-Methyl-, 77-6599

Lymphocyte Depletion

- Virus, Herpes Simplex
 - B-Lymphocytes, 77-6435
 - T-Lymphocytes, 77-6435

Lymphocyte Transformation

- DNA Replication
 - Inhibitory Factor, Isolation and Characterization 77-6469

Lymphocytes

- Aspergillus parasiticus*
 - Chromosome Abnormalities, 77-6176
 - Mitosis, 77-6176
- Aspergillus tamarii*
 - Mitosis, 77-6176
- Chromosome Aberrations
 - Radiation, Ionizing, 77-6078
- Ethyl Alcohol
 - Chromosome Aberrations, 77-6181
- Granuloma
 - Immune Response, 77-6470
- Hodgkin's Disease
 - DNA Replication, 77-6473
- Leukemia
 - Cholesterol, 77-6592
 - DNA Replication, 77-6592
 - Plant Agglutinins, 77-6592
- Lymphoma
 - Complement, 77-6471
 - Immunoglobulins, Fc, 77-6471
 - Immunoglobulins, Surface, 77-6471
 - Receptors, 77-6471
- Lymphoma, Lymphocytic
 - Complement, 77-6471
 - Erythrocytes, 77-6471
 - Immunoglobulins, Fc, 77-6471
 - Immunoglobulins, Surface, 77-6471
 - Receptors, 77-6471
- Plant Agglutinins
 - Cholesterol, 77-6592
 - DNA Replication, 77-6592
- Smoking
 - Aryl Hydrocarbon Hydroxylases, 77-6193
- Tars
 - Aryl Hydrocarbon Hydroxylases, 77-6193
- Trypsin
 - Immune Response, 77-6470
- Virus, Bovine Leukemia
 - Antigens, Viral, 77-6087
- Virus, Epstein-Barr
 - Cell Transformation, Neoplastic, 77-6407
 - Cells, Cultured, 77-6406
 - DNA Replication, 77-6407

B-Lymphocytes

- Antibody Formation
 - Chick Embryo, 77-6452
- Burkitt's Lymphoma

B-Lymphocytes (cont'd)

- Surface Properties, 77-6565
- Virus, Epstein-Barr, 77-6565
- Cell Differentiation
 - Chick Embryo, 77-6452
 - Immunosuppression, 77-6452
- Cyclophosphamide
 - Cell Differentiation, 77-6452
 - Chick Embryo, 77-6452
- Hodgkin's Disease
 - Surface Properties, 77-6565
- Immunoglobulins
 - Chick Embryo, 77-6452
- Infectious Mononucleosis
 - Surface Properties, 77-6565
- Leukemia
 - Immunoglobulins, Surface, 77-6477
- Leukemia, Lymphoblastic
 - Antigens, 77-6103
- Leukemia, Lymphocytic
 - Antigens, 77-6103
- Sarcoma, Reticulum Cell
 - Mouse, 77-6468
- Schistosoma mansoni*
 - DNA Replication, 77-6469
- Testosterone
 - Cell Differentiation, 77-6452
 - Chick Embryo, 77-6452
- Virus, Avian Leukosis
 - Antibody Formation, 77-6467
 - Cyclophosphamide, 77-6467
 - Histocompatibility Antigens, 77-6467
 - Immune Response, 77-6467
 - Viral Vaccines, 77-6467
- Virus, Bovine Leukemia
 - Syncytia Induction, 77-6332
 - Virus Replication, 77-6332
- Virus, Epstein-Barr
 - Baboon, 77-6413
- Virus, Friend Murine Leukemia
 - Viral Proteins, 77-6484
- Virus, Herpes Simplex
 - IgG, 77-6435
 - Lymphocyte Depletion, 77-6435

T-Lymphocytes

- Aging
 - Immune Response, 77-6097
- Antigens, Neoplasm
 - Immune Response, 77-6441
 - Immunity, Cellular, 77-6486
 - Migration Inhibitory Factor, 77-6486
- Antilymphocyte Serum
 - Rosette Formation, Chick, 77-6472
- BCG*
 - Transplantation Immunology, 77-6445
- Breast Neoplasms
 - Androgen Sulfates, 77-6531
- Carcinogen, Chemical
 - Immunosuppression, Review, 77-6100
- Fibrosarcoma
 - Transplantation Immunology, 77-6444
- Graft vs Host Reaction
 - Histocompatibility Antigens, 77-6449
 - Immunosuppression, 77-6449
- Leukemia, Lymphoblastic
 - Antigens, 77-6103
 - Surface Properties, 77-6565

T-Lymphocytes (cont'd)

- Leukemia, Lymphocytic
 - Antigens, 77-6103
 - Virus, Gross Murine Leukemia, 77-6560
- Lung Neoplasms
 - Immune Response, 77-6442
 - Transplantation Immunology, 77-6442
- Lymphosarcoma
 - Case Report, 77-6556
 - Surface Markers, 77-6556
- Macrophages
 - Migration Inhibitory Factor, 77-6486
- Mammary Neoplasms, Experimental
 - Immune Response, 77-6443
- Neoplasms, Experimental
 - Antilymphocyte Serum, 77-6448
 - Cholanthrene, 3-Methyl-, 77-6448
 - Immunosuppression, 77-6447, 77-6448
 - Neoplasm Metastasis, 77-6447
 - Transplantation Immunology, 77-6447, 77-6448
 - Virus, SV40, 77-6448
- Sarcoidosis
 - Immune Response, 77-6446
- Sarcoma
 - BCG*, 77-6445
 - Cholanthrene, 3-Methyl-, 77-6451
- Schistosoma mansoni*
 - DNA Replication, 77-6469
- Virus, Adeno 3
 - Antilymphocyte Serum, 77-6334
- Virus, Gross Murine Leukemia
 - Cell Transformation, Neoplastic, 77-6560
- Virus, Herpes Simplex
 - IgG, 77-6435
 - Immunity, Cellular, 77-6435
 - Lymphocyte Depletion, 77-6435
- Virus, Moloney Murine Sarcoma
 - Macrophages, 77-6486
 - Migration Inhibitory Factor, 77-6486

Lymphoepithelioma

see Carcinoma, Epidermoid

Lymphoid Tissue

- Age Factors
 - Rosette Formation, Chick, 77-6472
- Anti-Antibodies
 - Rosette Formation, Chick, 77-6472
- Cytochalasin B
 - Rosette Formation, Chick, 77-6472
- Erythrocytes
 - Rosette Formation, Chick, 77-6472
- Hyaluronidase
 - Rosette Formation, Chick, 77-6472
- Neuraminidase
 - Rosette Formation, Chick, 77-6472
- Pronase
 - Rosette Formation, Chick, 77-6472
- Trypsin
 - Rosette Formation, Chick, 77-6472
- Vincalukoblastine, Sulfate
 - Rosette Formation, Chick, 77-6472

Lymphoma

- Aflatoxin B1
 - Corticotropin, 77-6174
- Cells, Cultured
 - Cell Adherence, 77-6590

Lymphoma (cont'd)

- Cell Division, 77-6590
- Cytotoxicity Tests, Immunologic, 77-6437
- Cholanthrene, 3-Methyl-
 - Transplantation Immunology, 77-6455
- Epidemiology, 77-6530
 - Review, 77-6125
- Guanidine, Dodecyl-, Acetate
 - Mouse, 77-6274
 - Nitrous Acid, Sodium Salt, 77-6274
- Guanidine, Methyl-
 - Mouse, 77-6274
 - Nitrous Acid, Sodium Salt, 77-6274
- Heavy Chain Disease
 - Histological Study, 77-6474
- Histocompatibility Antigens
 - Tumor Dormancy, 77-6455
- Horizontal Transmission
 - Epidemiology, 77-6570
- Hydantoin, 5,5-Diphenyl-
 - Review, 77-6060
- Immune Serums
 - Transplantation Immunology, 77-6458
- Immunity, Cellular
 - Mouse, 77-6450
- Lymphocytes
 - Complement, 77-6471
 - Immunoglobulins, Fc, 77-6471
 - Immunoglobulins, Surface, 77-6471
 - Receptors, 77-6471
- Mitomycin C
 - Transplantation, Immunology, 77-6455
- Neoplasm Transplantation
 - Tumor Dormancy, 77-6455
- Resorcinol
 - Mouse, 77-6042
- Sarcoma, Reticulum Cell
 - Epidemiology, 77-6125
- Viral Vaccines
 - Transplantation Immunology, 77-6458
- Virus, Murine Leukemia
 - Transplantation Immunology, 77-6458
- Virus, Radiation Leukemia
 - Isolation and Characterization, 77-6345
 - Mouse, 77-6345

Lymphoma, Giant Follicular

- Chromosome Aberrations
 - Case Report, 77-6554
 - Chromosomes, Human, 13-15, 77-6554

Lymphoma, Lymphocytic

see Lymphosarcoma

Lymphosarcoma

- Acetic Acid, Ester with 2,6-Dimethyl-*m*-dioxan-4-ol
 - Rat, 77-6048
- Caffeine
 - Dose-Response Study, Rat, 77-6290
 - Methane, Dichloro-, 77-6290
- Hydroxylamine, *N*-2-Naphthyl-
 - Rat, 77-6286
- Lymphocytes
 - Complement, 77-6471
 - Erythrocytes, 77-6471
 - Immunoglobulins, Fc, 77-6471
 - Immunoglobulins, Surface, 77-6471
 - Receptors, 77-6471
- T-Lymphocytes

Lymphosarcoma (cont'd)

- Case Report, 77-6556
- Surface Markers, 77-6556
- Naphthalene, 1-Nitroso-
 - Rat, 77-6286
- Naphthalene, 2-Nitroso-
 - Rat, 77-6286
- Urea, Methyl Nitroso-
 - Histological Study, Guinea Pig, 77-6277

Macrophages

- Asbestos
 - Immune Response, 77-6465
- Carcinogen, Chemical
 - Immunosuppression, Review, 77-6100
- Fibrosarcoma
 - Immunity, Cellular, 77-6461
- Immunity, Cellular, 77-6459
- Lung Neoplasms
 - Smoking, 77-6189
- T-Lymphocytes
 - Migration Inhibitory Factor, 77-6486
- Migration Inhibitory Factor
 - Plasminogen, 77-6464
- Mycobacterium bovis*
 - Endocytosis, 77-6462
- Neoplasm Transplantation
 - Neoplasm Metastasis, 77-6463
- Smoking, 77-6511
 - Agglutination, 77-6192
 - Aryl Hydrocarbon Hydroxylases, 77-6192, 77-6193
 - Bronchi, 77-6511
 - Cell Survival, 77-6187
 - Cellular Inclusions, 77-6192
 - Concanavalin A, 77-6192
 - Immunity, Cellular, 77-6192
 - Ultrastructural Study, 77-6192, 77-6511
- Tars
 - Aryl Hydrocarbon Hydroxylases, 77-6193
- Toxoplasma gondii*
 - Endocytosis, 77-6462
- Virus, Moloney Murine Sarcoma
 - Histocompatibility Antigens, 77-6486
 - T-Lymphocytes, 77-6486
- Virus, Rauscher Murine Leukemia
 - Immune Response, 77-6466
 - Leukocyte Sequestration, 77-6466
 - Phagocytosis, 77-6466

Maleic Acid, Diethyl Ester

- Benzo(a)pyrene
 - DNA, Binding, 77-6204
 - Metabolism, Rat, 77-6204

Maleic Hydrazine

see 3,6-Pyridazinedione, 1,2-Dihydro-

Mammary Neoplasms, Experimental

- T-Lymphocytes
 - Immune Response, 77-6443
- Acetanilide, 4'-(*p*-Fluorophenyl)-
 - Nephrectomy, 77-6134
- Adenocarcinoma
 - Precancerous Conditions, 77-6229
 - Virus, Murine Mammary Tumor, 77-6372
- Adenofibroma
 - Acetic Acid, 2,4-Dichlorophenoxy-, 77-6052
 - Caffeine, 77-6290
- Adenoma

Mammary Neoplasms, Experimental (cont'd)

- DU 41274, 77-6239
- Benz(a)anthracene, 7,12-Dimethyl-
 - Histological Study, 77-6529
 - Precancerous Conditions, 77-6203
 - Tissue Extracts, Liver, Fetus, 77-6457
- Benzo(a)pyrene
 - Histological Study, 77-6528
- Caffeine
 - Dose-Response Study, Rat, 77-6290
 - Methane, Dichloro-, 77-6290
- Carcinogen, Chemical
 - Precancerous Conditions, 77-6111
- Carcinoma
 - Acetanilide, 4'-(p-Fluorophenyl)-, 77-6134
 - Dog, Review, 77-6038
- Cells, Cultured
 - Immune Response, 77-6443
- Cholanthrene, 3-Methyl-
 - Histological Study, 77-6528
- Contraceptives, Oral
 - Dog, Review, 77-6038
- Dietary Fats
 - Estrogens, 77-6234
 - Prolactin, 77-6234
- DU 41274
 - Contraceptives, Oral, 77-6239
- Estradiol
 - Neoplasm Transplantation, 77-6203
 - Precancerous Conditions, 77-6229
 - Strain Difference, Mouse, 77-6229
 - Ultrastructural Study, Mouse, 77-6229
- Estrogens
 - Animal Model, Mouse, 77-6232
- Estrone
 - Histological Study, 77-6528
- Fluorescein, 2',4',5',7'-Tetrabromo-, Disodium Salt
 - Adenofibroma, 77-6055
 - Fibrosarcoma, 77-6055
- Galactosyltransferases
 - Cell Membrane, 77-6480
 - Neoplasm Metastasis, 77-6480
- Glycoproteins
 - Antigen Shedding, 77-6480
 - Neoplasm Metastasis, 77-6480
- Growth Substances
 - Tissue Extracts, Liver, Fetus, 77-6457
- Hyperplasia
 - DU 41274, 77-6239
- Insulin
 - Neoplasm Transplantation, 77-6203
- Ovary
 - Animal Model, Mouse, 77-6232
 - Transplantation, Homologous, 77-6232
- Precancerous Conditions
 - Neoplasm Transplantation, 77-6203
- Progesterone
 - Dog, Review, 77-6038
 - Dose-Response Study, Mouse, 77-6235
 - Estrogens, 77-6235
 - Neoplasm Transplantation, 77-6203
 - Prolactin, 77-6235
- Prolactin
 - Neoplasm Transplantation, 77-6203
- Propane, 1,2-Dibromo-3-chloro-
 - Carcinoma, 77-6044
 - Rat, 77-6044

Mammary Neoplasms, Experimental (cont'd)

- Sarcoma
 - Dog, Review, 77-6038
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Strain Difference, Mouse, 77-6229
- Urea, Methyl Nitroso-
 - Dietary Fats, 77-6234
- Virus, Murine Mammary Tumor
 - Genotype, 77-6372
 - Histological Study, 77-6372
 - Precancerous Conditions, 77-6111
 - Pregnancy, 77-6372
- Virus, RNA Tumor
 - Mouse, 77-6341
- Manganese
 - RNA Polymerase
 - Carcinogenic Potential, 77-6217
- Marek's Disease
 - Histocompatibility Antigens
 - Chicken, 77-6327
 - Genetics, 77-6327
- Melanoma
 - Alanine, 3-(3,4-Dihydroxyphenyl)-
 - Review, 77-6060
 - Carcinoembryonic Antigen
 - Antibody Specificity, 77-6485
 - Cell Membrane, 77-6485
 - Isolation and Characterization, 77-6485
 - Cell Membrane
 - Glycoproteins, 77-6589
 - Cells, Cultured
 - Glycoproteins, 77-6589
 - Glycoproteins
 - Antigen Shedding, 77-6589
 - Isolation and Characterization, 77-6589
 - Nose Neoplasms
 - Epidemiology, 77-6579
 - Trypsin
 - Glycoproteins, 77-6589
 - Uridine, 5-Bromo-2'-deoxy-
 - Virus Replication, 77-6153
 - Uridine, 2'-Deoxy-5-iodo-
 - Virus Replication, 77-6153
 - Wood
 - Epidemiology, 77-6580
- Melphalan
 - see Alanine, 3-(p-(Bis(2-chloroethyl)amino)phenyl)-
- Meningioma
 - Brain Neoplasms
 - Ultrastructural Study, 77-6547
- Menopause
 - Ovarian Neoplasms
 - Premarin, 77-6228
 - 4,4-Stilbenediol, α,α' -Diethyl-, 77-6228
- 6-Mercaptopurine
 - see Purine-6-thiol
- Mercury
 - Water Pollution
 - Isolation and Characterization, 77-6585
 - Review, 77-6025
- Mesothelioma
 - Asbestos
 - Bronchial Neoplasms, 77-6578

- Mesothelioma (cont'd)**
 Lung Neoplasms, 77-6578
 Lung Neoplasms
 Asbestos, 77-6577
 Peritoneal Neoplasms
 Asbestos, 77-6073, 77-6113
 Pleural Neoplasms
 Asbestos, 77-6073, 77-6113
- Mestranol**
 Liver
 Carcinogenic Metabolite, 77-6035
 Metabolism, 77-6035
- Metals**
 Carcinogen, Environmental
 Carcinogenic Potential, 77-6217
 RNA Polymerase, 77-6217
 RNA Polymerase
 Mutagenic Activity, 77-6217
- Metaplasia**
 Laryngeal Neoplasms
 Smoking, 77-6188
 Ultrastructural Study, Rat, 77-6188
- Methane, Diazo-**
 Guanosine
 Methylation Products, 77-6275
- Methane, Dichloro-**
 Adrenal Gland Neoplasms
 Caffeine, 77-6290
 Caffeine
 Carcinogenic Activity, 77-6290
 Lymphosarcoma
 Caffeine, 77-6290
 Mammary Neoplasms, Experimental
 Caffeine, 77-6290
 Nephroblastoma
 Caffeine, 77-6290
- Methane, Sulfinylbis-**
 Virus, Friend Murine Leukemia
 Cell Differentiation, 77-6355
- Methanesulfonic Acid, Methyl Ester**
 Carbamic Acid, Diethyldithio-
 DNA, Liver, 77-6254
 DNA Repair
 Cells, Cultured, 77-6005
 Rat, 77-6257
- Methanol, (Methyl-*ONN*-azoxy)-, Acetate (Ester)**
 Carbamic Acid, Diethyldithio-
 DNA, Liver, 77-6254
 Liver Neoplasms
 Fish, 77-6143
 Histological Study, 77-6143
- Methotrexate**
 Cell Transformation, Neoplastic
 Embryo, Rat, 77-6294
 DNA Repair
 Spleen, Rat, 77-6293
 Ultraviolet Rays
 Spleen, Rat, 77-6293
 Virus, Pox
 Virus Replication, 77-6294
- Methylamine, *N*-Nitroso-**
 Models, Theoretical
- Methylamine, *N*-Nitroso- (cont'd)**
 Carcinogenic Potential, 77-6268
- Methylenediamine, *N,N'*-Dimethyl-*N,N'*-dinitroso-**
 Cell Transformation, Neoplastic
 Dose-Response Study, 77-6013
- O*⁶-Methylguanine**
 see Purine, 2-Amino-6-methoxy-
- Methylnitrosourethane**
 see Carbamic Acid, *N*-Methyl-*N*-nitroso-
- Mibolerone**
 see Estr-4-en-3-one, 7 α ,17-Dimethyl-17 β -Hydroxy
- Microsomes**
 7,8-Benzoflavone
 Metabolism, 77-6180
 Liver Neoplasms
 Lipids, 77-6210
 Phospholipids, 77-6210
- Microsomes, Liver**
 Benzene, 4-Allyl-1,2-(methylenedioxy)-
 Metabolism, 77-6150
 4,4'-Biphenyldiol
 Biphenyl, 77-6148
 Quantitation Method, 77-6148
 2-Biphenylol
 Biphenyl, 77-6148
 Quantitation Method, 77-6148
 3-Biphenylol
 Biphenyl, 77-6148
 Quantitation Method, 77-6148
 4-Biphenylol
 Biphenyl, 77-6148
 Quantitation Method, 77-6148
 Chrysene, 1,2-Dihydro-1,2-dihydroxy-
 Mutagenic Activity, 77-6202
 Ellipticine
 Cytochrome P-450, 77-6206
 Cytochromes, 77-6206
 Hydroxylases, 77-6206
 Ethylene, Chloro-
 Metabolism, 77-6157
 Nucleic Acids, 77-6157
- Migration Inhibitory Factor**
 T-Lymphocytes
 Antigens, Neoplasm, 77-6486
 Macrophages
 Plasminogen, 77-6464
 Virus, Moloney Murine Sarcoma
 Histocompatibility Antigens, 77-6486
 T-Lymphocytes, 77-6486
 Virus, SV40
 Cell Transformation, Neoplastic, 77-6464
- Mineral Oil**
 see Petroleum
- Mirex**
 Liver Neoplasms
 Carcinoma, 77-6050
- Mitochondria**
 Acetamide, Thio-
 Ligases, 77-6133
 Liver, 77-6133
 Ornithine Carbamoyltransferase, 77-6133
 Carcinogen, Chemical

- Mitochondria (cont'd)**
 Oxidative Phosphorylation, 77-6165
 Liver
 Rat, 77-6133
 Liver Neoplasms
 Lipids, 77-6210
 Phospholipids, 77-6210
- Mitomycin**
 Chromosome Aberrations
 Mouse, 77-6292
- Mitomycin C**
 Lymphoma
 Transplantation, Immunology, 77-6455
 Ultraviolet Rays
 DNA Repair, 77-6293
 Virus, SV40
 Virus Replication, 77-6415
- Mitosis**
Aspergillus parasiticus
 Lymphocytes, 77-6176
Aspergillus tamaritii
 Lymphocytes, 77-6176
- Mitration Inhibitory Factor**
 T-Lymphocytes
 Macrophages, 77-6486
- Monoamine Oxidase**
 Prostatic Neoplasms
 Carcinoma, Epidermoid, 77-6247
- Monocytes**
 Fibrosarcoma
 Transplantation Immunology, 77-6444
- Mouth Neoplasms**
 Alcohol Drinking
 Diagnosis and Prognosis, 77-6183
 Carcinoma, Epidermoid
 Ultrastructural Study, 77-6519
 Myoblastoma
 Histological Study, 77-6546
 Ultrastructural Study, 77-6545, 77-6546
 Smoking
 Diagnosis and Prognosis, 77-6183
 Epidemiology, 77-6123
 Tobacco
 Epidemiology, Review, 77-6124
- Multiple Myeloma**
 Bence Jones Protein
 Temperature Dependence, 77-6476
 IgG
 Temperature Dependence, 77-6476
 Immunoglobulins, Fc
 Temperature Dependence, 77-6476
 Immunoglobulins, Light Chain
 Temperature Dependence, 77-6476
 Wood
 Epidemiology, 77-6580
- Muramidase**
 Granuloma
 Carrageen, 77-6289
- Mutagens**
 Carcinogenic Potential
 Review, 77-6001
 Water Pollution
- Mutagens (cont'd)**
 Carcinogenic Potential, Review, 77-6026
- Mutation**
 Carcinogen, Chemical
 Screening Methods, Review, 77-6011
- Myasthenia Gravis**
 Breast Neoplasms
 Epidemiology, 77-6531
 Neoplasms, Multiple Primary, 77-6531
 Precancerous Conditions, 77-6531
- Mycobacterium bovis**
 Erythrocytes
 Endocytosis, 77-6462
 Fibrosarcoma
 Transplantation Immunology, 77-6444
 Hemoglobins
 Endocytosis, 77-6462
 Macrophages
 Endocytosis, 77-6462
 Virus, Adeno 3
 Immune Response, 77-6334
- Mycotoxins**
Aspergillus parasiticus
 Chromosome Abnormalities, 77-6176
 Liver Neoplasms
 Carcinoma, 77-6036
 Oxidoreductases
 Review, 77-6009
- Myeloma Proteins**
 Immune Response
 Mouse, 77-6478
 Plasmacytoma
 Antigenic Determinants, 77-6479
- Myeloproliferative Disorders**
 Leukemia
 Precancerous Conditions, Review, 77-6105
- Myoblastoma**
 Mouth Neoplasms
 Histological Study, 77-6546
 Ultrastructural Study, 77-6545, 77-6546
- Myosin**
 Neuroglia
 Isolation and Characterization, 77-6421
 Virus, SV40
 Cell Transformation, Neoplastic, 77-6421
 Neuroglia, 77-6421
 Phosphotransferases, 77-6421
 Temperature Sensitive Mutants, 77-6421
- Nafenopin**
 Pancreatic Neoplasms
 Carcinoma, 77-6285
- Naphthalene, 1-Nitroso-**
 Colonic Neoplasms
 Adenocarcinoma, 77-6286
 Lymphosarcoma
 Rat, 77-6286
- Naphthalene, 2-Nitroso-**
 Lung Neoplasms
 Adenoma, 77-6286
 Lymphosarcoma
 Rat, 77-6286

Naphthalenemethanol, α -((Isopropylamino)methyl)-
Liver
Carcinogenic Potential, Mouse, 77-6241

1-Naphthylamine
Skin Neoplasms
Rat, 77-6286

2-Naphthylamine
Skin Neoplasms
Rat, 77-6286

Nasopharyngeal Neoplasms
Carcinoma
Antibodies, Viral, 77-6404
Virus, Epstein-Barr, 77-6404, 77-6412
DNA, Viral
Nucleic Acid Hybridization, 77-6404
Genetics
Case Report, 77-6512
Histocompatibility Antigens
Epidemiology, Review, 77-6094
Immune Response, Review, 77-6096
Virus, Epstein-Barr
Antibodies, Viral, 77-6404
Antigen-Antibody Reactions, 77-6403
Epidemiology, 77-6403

Neoplasm Metastasis
Breast Neoplasms
Epidemiology, Japan, US, 77-6573
Carcinoma, Bronchogenic
Cell Line, 77-6509
Carcinoma, Epidermoid
Burns, 77-6518
Carcinoma, Oat Cell
Cell Line, 77-6509
Cervix Neoplasms
Carcinoma, Epidermoid, 77-6524
Epidemiology, Puerto Rico, 77-6572
Epidemiology, United States, 77-6572
Gynecologic Neoplasms
Cell Cycle Kinetics, 77-6576
Head and Neck Neoplasms
Hodgkin's Disease, 77-6549
Sarcoma, 77-6549
Liver Neoplasms
Case Report, 77-6507
Lung Neoplasms
Neurilemmoma, 77-6544
Macrophages
Neoplasm Transplantation, 77-6463
Mammary Neoplasms, Experimental
Galactosyltransferases, 77-6480
Glycoproteins, 77-6480
Neoplasms, Experimental
T-Lymphocytes, 77-6447
Radiation, Ionizing, 77-6447
Thymus Gland, 77-6447
Platelet Aggregation
Bencyclane, 77-6549
Dipyridamole, 77-6549
Pentoxifylline, 77-6549
Respiratory Tract Neoplasms
Ethenamine, N-Ethylene-N-nitroso-, 77-6248
Sarcoma
Immunity, Cellular, 77-6451
Transplantation Immunology, 77-6451
Sweat Gland Neoplasms

Neoplasm Metastasis (cont'd)
Carcinoma, Epidermoid, 77-6520
Urogenital Neoplasms
Ultrastructural Study, Crab, 77-6568

Neoplasm Transplantation
Fibrosarcoma
Immunity, 77-6454
Leukemia
Urea, Ethyl Nitroso-, 77-6279
Lymphoma
Tumor Dormancy, 77-6455
Macrophages
Neoplasm Metastasis, 77-6463
Mammary Neoplasms, Experimental
Estradiol, 77-6203
Insulin, 77-6203
Precancerous Conditions, 77-6203
Progesterone, 77-6203
Prolactin, 77-6203
Neoplasms, Experimental
Uridine, 5-Bromo-2'-deoxy-, 77-6153
Uridine, 2'-Deoxy-5-iodo-, 77-6153
Pancreatic Neoplasms
Rat, 77-6285
Virus, Marek's Disease Herpes
Chicken, 77-6328
Virus, RNA Tumor
Mouse, 77-6341

Neoplasms (General and Unspecified)
Anthracene
Epidemiology, 77-6200
Asbestos
Review, 77-6073
Automobile Exhaust
Epidemiology, 77-6200
Carcinoembryonic Antigen
Immunosuppression, 77-6099
Carcinogen, Environmental
Aquatic Animals, Review, 77-6023
Cell Division
Cell Cycle Kinetics, Review, 77-6128
Child
Epidemiology, Review, 77-6126
Chromosome Aberrations
Review, 77-6107
Chrysene, 5-Methyl-
Epidemiology, 77-6200
Fetal Globulins
Immunosuppression, 77-6099
Histocompatibility Antigens
Epidemiology, 77-6099
Immunologic Deficiency Syndromes
Review, 77-6099
Leukemia, Myelocytic
Review, 77-6107
Polycyclic Hydrocarbons
Automobile Exhaust, 77-6200
Epidemiology, 77-6200
Pyrene
Epidemiology, 77-6200
Radiation, Ionizing
Epidemiology, 77-6084
Virus, Papova
Antibodies, Viral, 77-6383

Neoplasms, Connective Tissue
Water Pollution

- Neoplasms, Connective Tissue (cont'd)**
Epidemiology, Crab, 77-6568
- Neoplasms, Experimental**
Benz(a)anthracene, 7,12-Dimethyl-
Transplantation Immunology, 77-6447
Cholanthrene, 3-Methyl-
Antigens, Neoplasm, 77-6099
T-Lymphocytes, 77-6448
Transplantation Immunology, 77-6448
Chromosome Aberrations
Review, 77-6107
Immunity, Cellular
Isotope Release Assay, 77-6434
T-Lymphocytes
Antilymphocyte Serum, 77-6448
Immunosuppression, 77-6447, 77-6448
Neoplasm Metastasis, 77-6447
Transplantation Immunology, 77-6447, 77-6448
Radiation, Ionizing
Neoplasm Metastasis, 77-6447
Thymus Gland
Neoplasm Metastasis, 77-6447
Uridine, 5-Bromo-2'-deoxy-
Neoplasm Transplantation, 77-6153
Virus Replication, 77-6153
Uridine, 2'-Deoxy-5-iodo-
Neoplasm Transplantation, 77-6153
Virus Replication, 77-6153
Virus, Adeno 7 - SV40 Hybrid
Antigen-Antibody Reactions, 77-6439
Immunity, Cellular, 77-6439
Virus, SV40
T-Lymphocytes, 77-6448
Transplantation Immunology, 77-6448
- Neoplasms, Multiple Primary**
Breast Neoplasms
Androgen Sulfates, 77-6531
Myasthenia Gravis, 77-6531
Carcinogen, Environmental
Cell Transformation, Neoplastic, 77-6101
Carcinoma, Epidermoid
Case Report, 77-6522
Colonic Neoplasms
Genetics, 77-6506
Cylindroma
Ultrastructural Study, 77-6523
Hepatoma
Androsta-1,4-dien-3-one, 17-Hydroxy-17-methyl-
77-6244
Hereditary Diseases
Cell Transformation, Neoplastic, 77-6101
Intestinal Neoplasms
Adenocarcinoma, 77-6550
Case Report, 77-6550
Liver Neoplasms
Androsta-1,4-dien-3-one, 17-Hydroxy-17-methyl-
77-6244
Retinoblastoma
Case Report, 77-6551
Genetics, 77-6551
Thyroid Neoplasms
Adenocarcinoma, 77-6543
Carcinoma, Papillary, 77-6543
Goiter, 77-6543
Nervous System Neoplasms, 77-6543
Urogenital Neoplasms
- Neoplasms, Multiple Primary (cont'd)**
Case Report, 77-6551
Genetics, 77-6551
- Neoplasms, Vascular Tissue**
Phenylhydrazine, 4-Hydroxymethyl-
Carcinogenic Potential, Mouse, 77-6172
- Nephroblastoma**
Caffeine
Dose-Response Study, Rat, 77-6290
Methane, Dichloro-, 77-6290
- Nervous System Neoplasms**
Thyroid Neoplasms
Brachial Plexus, 77-6543
Case Report, 77-6543
Neoplasms, Multiple Primary, 77-6543
Urea, Ethyl Nitroso-
Carcinogenic Activity, 77-6069
Urea, Methyl Nitroso-
Carcinogenic Activity, 77-6069
- Neuraminidase**
Lymphoid Tissue
Rosette Formation, Chick, 77-6472
- Neurilemmoma**
Brain Neoplasms
Histological Study, 77-6002
Cell Line
Isolation and Characterization, 77-6544
Lung Neoplasms
Neoplasm Metastasis, 77-6544
Transplantation, Heterologous, 77-6544
Thyroid Neoplasms
Case Report, 77-6543
- Neuroblastoma**
Hydantoin, 5,5-Diphenyl-
Review, 77-6060
- Neuroepithelioma**
Case Report
Histological Study, 77-6548
Pineal Body
Histological Study, 77-6548
- Neurofibroma**
Thyroid Neoplasms
Case Report, 77-6543
- Neuroglia**
Myosin
Isolation and Characterization, 77-6421
Virus, SV40
Myosin, 77-6421
- Neutral Red**
Salmonella typhimurium
Mutagenic Activity, 77-6306
- Nickel**
Nose Neoplasms
Epidemiology, Norway, 77-6581
Occupational Hazard, 77-6581
- Nicotine, 1'-Nitroso-1'-demethyl-**
Tobacco
Quantitation Method, 77-6185
- Nitric Acid**
DNA
Mutagenic Activity, 77-6067

- Nitric Acid (cont'd)**
Metabolism
Toxicology, 77-6066
- Nitric Acid, Sodium Salt**
Piperazine, 1,4-Dinitroso-
Carcinogenic Activity, Mouse, 77-6269
- Nitrite**
see Nitrous Acid
- Nitrogen Mustard**
Carcinogen, Chemical
Review, 77-6001
Mutagenic Activity
Review, 77-6001
Teratogens
Review, 77-6001
- Nitrosamines**
Ascorbic Acid
Stomach Neoplasms, 77-6064
Bladder Neoplasms
Schistosomiasis, 77-6266
Urinary Tract Infections, 77-6266
Urine, Isolation and Characterization, 77-6266
Marine Organisms
Metabolism, Review, 77-6024
Models, Theoretical
Carcinogenic Potential, 77-6268
- Nitrous Acid**
Diethylamine, *N*-Nitroso-
Carcinogenic Activity, 77-6063
Mutagenic Activity, 77-6063
Dimethylamine, *N*-Nitroso-
Carcinogenic Activity, 77-6063
Mutagenic Activity, 77-6063
DNA
Mutagenic Activity, 77-6067
Metabolism
Toxicology, 77-6066
Stomach Neoplasms
Epidemiology, 77-6068
Precancerous Conditions, 77-6068
Water Pollution, 77-6068
- Nitrous Acid, Sodium Salt**
Hepatoma
Guanidine, Dodecyl-, Acetate, 77-6274
Guanidine, Methyl-, 77-6274
Lymphoma
Guanidine, Dodecyl-, Acetate, 77-6274
Guanidine, Methyl-, 77-6274
- Norepinephrine**
Prostatic Neoplasms
Carcinoma, Epidermoid, 77-6247
- Nose Neoplasms**
Adenocarcinoma
Epidemiology, 77-6113, 77-6579
Carcinoma
Epidemiology, 77-6579
Melanoma
Epidemiology, 77-6579
Nickel
Epidemiology, Norway, 77-6581
Occupational Hazard, 77-6581
- Nose Neoplasms (cont'd)**
Occupational Hazard
Epidemiology, Norway, 77-6581
2-Propanol, 1,1'-Iminodi-*N*-nitroso-
Carcinogenic Activity, Hamster, 77-6264
Wood
Epidemiology, 77-6579
- Nucleic Acids**
Alylating Agents
Mutagenic and Carcinogenic Activity, Review
77-6006
Ethylene, Chloro-
Microsomes, Liver, 77-6157
Poly A, 77-6157
Ribonucleotides, 77-6157
- Nucleotides**
Cell Transformation, Neoplastic
Hypoxanthine Phosphoribosyltransferase, 77-6595
Virus, SV40
Cell Transformation, Neoplastic, 77-6595
- Occupational Hazard**
Leukemia, Monoblastic
Benzene, 77-6145
Leukemia, Myeloblastic
Benzene, 77-6145
Lung Neoplasms
Epidemiology, Review, 77-6127
Ether Chloromethyl Methyl, 77-6071
Nose Neoplasms
Epidemiology, Norway, 77-6581
Nickel, 77-6581
Petroleum
Mutagenic Activity, 77-6225
Radium
Epidemiology, 77-6300
Selenium
Toxicology, Review, 77-6076
Tellurium
Toxicology, Review, 77-6076
- Oligodendroglioma**
Brain Neoplasms
Histological Study, 77-6002
Plants, 77-6173
- Oncogenic Viruses**
Carcinogen, Environmental
Co-carcinogenic Activity, Review, 77-6102
Genetics, Human
Review, 77-6086
- Ornithine Carbamoyltransferase**
Acetamide, Thio-
Mitochondria, 77-6133
- Osteosarcoma**
see Sarcoma, Osteogenic
- Ovarian Neoplasms**
Carcinoma
Case Report, 77-6525
Chromosome Aberrations, 77-6527
Histological Study, 77-6525
Disgerminoma
Histological Study, Fish, 77-6526
Estrogens
Epidemiology, 77-6231

Ovarian Neoplasms (cont'd)

- Fibroma
 - Histological Study, Fish, 77-6526
- Granulosa Cell Tumor
 - Histological Study, Fish, 77-6526
- Premarin
 - Epidemiology, 77-6228
 - Menopause, 77-6228
- Radiation, Ionizing
 - Virus-Like Particles, 77-6342
- 4,4-Stilbenediol, α,α' -Diethyl-
 - Epidemiology, 77-6228
 - Menopause, 77-6228
 - Premarin, 77-6228
- Teratoid Tumor
 - Histological Study, Fish, 77-6526
- Urea, Ethyl Nitroso-
 - Transplacental Carcinogenesis, 77-6280
- Virus-Like Particles
 - Ultrastructural Study, 77-6342

Ovary

- Mammary Neoplasms, Experimental
 - Animal Model, Mouse, 77-6232
 - Transplantation, Homologous, 77-6232

2-Oxetanone

- Adenine, 1-(2-Carboxyethyl)-
 - DNA, 77-6240
 - Isolation and Characterization, 77-6240
- DNA
 - Adenine Derivatives, 77-6240
 - Binding, Liver, Thymus, 77-6240

Oxidoreductases

- Barbituric Acid, 5-Ethyl-5-phenyl-
 - Review, 77-6009
- Carcinogen, Chemical
 - Review, 77-6009
- Dimethylamine, *N*-Nitroso-
 - Review, 77-6009
- Mycotoxins
 - Review, 77-6009
- Polychlorobiphenyl Compounds
 - Enzymatic Activity, Review, 77-6015
- Polycyclic Hydrocarbons
 - Review, 77-6009

Oxymetholone

- Liver Neoplasms
 - Histological Study, 77-6513

Ozone

- Water Pollution
 - Carcinogenic Potential, Review, 77-6026

Pancreatic Neoplasms

- Adenocarcinoma
 - Morpholine, 2,6-Dimethyl-*N*-nitroso-, 77-6270
- Adenoma
 - Propanol, 1,1'-Iminodi-*N*-nitroso-, 77-6265
- Androgens
 - Case Report, 77-6246
 - Histological Study, 77-6246
- Carcinoma
 - Adenocarcinoma, 77-6270
 - Histological Study, 77-6285
 - Nafenopin, 77-6285
 - Propanol, 1,1'-Iminodi-*N*-nitroso-, 77-6265
 - Ultrastructural Study, 77-6285

Pancreatic Neoplasms (cont'd)

- Ethenamine, *N*-Ethylene-*N*-nitroso-
 - Carcinogenic Potential, Hamster, 77-6248
- Hepatoma
 - Androgens, 77-6246
- Morpholine, 2,6-Dimethyl-*N*-nitroso-
 - Histological Study, Hamster, 77-6270
 - Neoplasm Metastasis, 77-6270
- Neoplasm Transplantation
 - Rat, 77-6285
- Prednisone
 - Case Report, 77-6246
- 2-Propanol, 1,1'-Iminodi-*N*-nitroso-
 - Carcinogenic Activity, Hamster, 77-6264
 - Carcinogenic Activity, Rat, 77-6263
- Serine, Diazoacetate (Ester)
 - Animal Model, Rat, 77-6166
 - Dose-Response Study, 77-6166
 - Precancerous Conditions, 77-6166
 - Species Difference, 77-6166
- Testosterone
 - Case Report, 77-6246

Papilloma

- Benzene, 1,4-Bis(chloromethoxymethyl)-
 - Skin Neoplasms, 77-6043
- p*-Benzoquinone
 - Skin Neoplasms, 77-6049
- Bladder Neoplasms
 - 1-Butanol, 4-(Butylnitrosamino)-, 77-6261
- 2-Butene, 1,4-Dichloro-
 - Skin Neoplasms, 77-6046
- Epidemiology
 - Fish, 77-6587
- Ethane, 1,2-Bis(chloromethoxy)-
 - Skin Neoplasms, 77-6047
- Histological Study
 - Fish, 77-6587
- Lip Neoplasms
 - Aquatic Animals, Review, 77-6023
- Lung Neoplasms
 - Smoking, 77-6189
- Skin Neoplasms
 - Benzo(a)pyrene, 77-6042
 - Fish, 77-6586
 - Propane, 1,2,3-Tris(chloromethoxy)-, 77-6045
 - Pyrocatechol, 77-6042
- Ultrastructural Study
 - Fish, 77-6587
- Virus, Shope Papilloma
 - Rabbit, 77-6496

Parathyroid Neoplasms

- Carcinoma
 - Genetics, 77-6539
- Genetics
 - Case Report, 77-6539
- Hyperparathyroidism
 - Genetics, 77-6539

Parity

- Breast Neoplasms
 - Epidemiology, 77-6116

Parotid Neoplasms

- Carcinoma
 - Case Report, 77-6535
 - Ultrastructural Study, 77-6535

- Pentoxifylline**
Neoplasm Metastasis
Platelet Aggregation, 77-6549
- Peptic Ulcer**
Stomach Neoplasms
Pathology, 77-6110
- Peptide Hydrolases**
Fibroblasts
Plasminogen Activators, 77-6596
- Peptides**
Virus, Adeno 2
Cell-Cycle Kinetics, 77-6391
Subcellular Fractions, HeLa Cells, 77-6391
Virus Replication, 77-6391
Virus, Rous Sarcoma
Cell Membrane, 77-6307
Cell Transformation, Neoplastic, 77-6307
Glucosamine, 77-6307
Glucose, 2-Deoxy-, 77-6307
- Peptidoglycan**
Fibrosarcoma
Cholanthrene, 3-Methyl-, 77-6459
Immunity, Cellular, 77-6459
Bacillus megaterium
Immunity, Cellular, 77-6459
- Peritoneal Neoplasms**
Mesothelioma
Asbestos, 77-6073, 77-6113
- Pesticides**
Bacteria
Degradation, Review, 77-6062
Water Pollution
Carcinogenic Potential, Review, 77-6022
- Petroleum**
Mutagenic Activity
Salmonella typhimurium, 77-6296
Occupational Hazard
Mutagenic Activity, 77-6225
Water Pollutants
Mutagenic Activity, 77-6296
- Phagocytes**
Granuloma
Carrageen, 77-6289
- Phagocytosis**
Virus, Rauscher Murine Leukemia
Macrophages, 77-6466
- Pharyngeal Neoplasms**
Smoking
Epidemiology, 77-6123
- Phenol, (1,1-Dimethylethyl)-4-methoxy-**
Guanidine, 1-Methyl-3-nitro-1-nitroso-
Guanyl Cyclase, 77-6273
- Phenol, 2-Methoxy-4-(2-propenyl)-**
Salmonella typhimurium
Mutagenic Activity, 77-6146
- Phenylhydrazine, 4-Hydroxymethyl-**
Lung Neoplasms
Carcinogenic Potential, Mouse, 77-6172
Neoplasms, Vascular Tissue
- Phenylhydrazine, 4-Hydroxymethyl- (cont'd)**
Carcinogenic Potential, Mouse, 77-6172
- Phorbol**
Liver Neoplasms
Acetamide, *N*-Fluoren-2-yl-, 77-6135
- Phosphatidyl Inositol**
Virus, Rous Sarcoma
Cell Transformation, Neoplastic, 77-6310
Metabolism, 77-6310
- Phospholipids**
Cell Membrane
Spin Labels, 77-6369
Liver Neoplasms
Microsomes, 77-6210
Mitochondria, 77-6210
- Phosphotransferases**
Virus, SV40
Myosin, 77-6421
- Pineal Body**
Neuroepithelioma
Histological Study, 77-6548
- Piperazine, 1,4-Dinitroso-**
Nitric Acid, Sodium Salt
Carcinogenic Activity, Mouse, 77-6269
- Pituitary Gland**
Biurea, 1-Methyl-6-(1-methylallyl)-2,5-dithio-
Histological Study, 77-6537
Ultrastructural Study, 77-6537
Fish
Histological Study, 77-6537
Ultrastructural Study, 77-6537
- Pituitary Neoplasms**
Adenoma, Chromophobe
Ultrastructural Study, 77-6536
- Plant Agglutinins**
Leukemia
Lymphocytes, 77-6592
Lymphocytes
Cholesterol, 77-6592
DNA Replication, 77-6592
- Plant Tumors**
Agrobacterium tumefaciens
DNA, Bacterial, 77-6131
- Plasmacytoma**
Cell Membrane
Antigenic Determinants, 77-6479
IgA
Antigens, Neoplasm, 77-6479
Histocompatibility Antigens, 77-6479
Immunoglobulins
Isolation and Characterization, 77-6475
Myeloma Proteins
Antigenic Determinants, 77-6479
Virus, Epstein-Barr
Case Report, 77-6557
Virus-Like Particles
RNA, Viral, 77-6348
- Plasminogen**
Cell Division
Fibroblasts, 77-6596

Plasminogen (cont'd)

- Cell Transformation, Neoplastic Fibroblasts, 77-6596
- Fibroblasts
 - Cells, Cultured, 77-6596
 - Culture Media, 77-6596
- Migration Inhibitory Factor Macrophages, 77-6464
- Peptide Hydrolases Fibroblasts, 77-6596
- Teratoid Tumor Virus, SV40, 77-6431

Platelet Aggregation

- Neoplasm Metastasis
 - Bencyclane, 77-6549
 - Dipyridamole, 77-6549
 - Pentoxifylline, 77-6549

Pleural Neoplasms

- Mesothelioma
 - Asbestos, 77-6073, 77-6113

Plutonium

- Americium
 - Dose-Response Study, 77-6075
- Bone and Bones
 - Dose-Response Study, 77-6075
- Gastrointestinal System
 - Dose-Response Study, 77-6075
- Lung
 - Dose-Response Study, 77-6075
- Water Pollution
 - Review, 77-6025

Plutonium Oxide

- Lung
 - Clearance, Translocation, 77-6224
- Sodium Oxide
 - Lung, 77-6224

Poly A

- Bacteriophages
 - RNA, Viral, 77-6320
- Ethylene, Chloro-
 - Nucleic Acids, 77-6157

Polychlorobiphenyl Compounds

- Aryl Hydrocarbon Hydroxylases
 - Enzymatic Activity, 77-6198
- Environmental Hazard
 - 77-6015
 - Toxicity, Review, 77-6015
- Gastric Mucosa
 - Hyperplasia, 77-6149
- Marine Organisms
 - Metabolism, Review, 77-6024
- Oxidoreductases
 - Enzymatic Activity, Review, 77-6015
- Stomach Neoplasms
 - Hyperplasia, 77-6149
- Water Pollution
 - Review, 77-6025

Polycyclic Hydrocarbons

- Automobile Exhaust
 - Carcinogenic Potential, Review, 77-6016
- Bacteria
 - Degradation, Review, 77-6062
- Carcinogenic Potential
 - Models, Theoretical, 77-6201

Polycyclic Hydrocarbons (cont'd)

- Marine Organisms
 - Metabolism, Review, 77-6024
- Neoplasms
 - Automobile Exhaust, 77-6200
 - Epidemiology, 77-6200
- Oxidoreductases
 - Review, 77-6009
- Water Pollution
 - Review, 77-6025

Polylysine

- Sarcoma
 - Mouse, 77-6600

Polyps

- Colonic Neoplasms
 - Carcinoma, 77-6109
 - Chromosome Aberrations, 77-6506
 - Genetics, 77-6506

Polyribosomes

- RNA
 - Liver Regeneration, 77-6593

Precancerous Conditions

- Breast Neoplasms
 - Hyperplasia, 77-6111
 - Myasthenia Gravis, 77-6531
- Bronchial Neoplasms
 - Animal Model, Dog, 77-6215
 - Benzo(a)pyrene, 77-6215
 - Urea, Methyl Nitroso-, 77-6215
- Carcinogen, Environmental
 - Immune Response, Review, 77-6102
- Colonic Neoplasms
 - Histological Study, 77-6502
- Esophageal Neoplasms
 - Diethylamine, *N*-Nitroso-, 77-6252
- Gynecologic Neoplasms
 - Estradiol, 77-6229
 - Testosterone, Propionate, 77-6245
- Laryngeal Neoplasms
 - Smoking, 77-6188
- Liver Neoplasms
 - Diethylamine, *N*-Nitroso-, 77-6251
- Lung Neoplasms
 - Cholanthrene, 3-Methyl-, 77-6195
 - Smoking, 77-6189, 77-6510
 - Transplantation, Heterologous, 77-6510
- Mammary Neoplasms, Experimental
 - Adenocarcinoma, 77-6229
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-6203
 - Carcinogen, Chemical, 77-6111
 - Estradiol, 77-6229
 - Neoplasm Transplantation, 77-6203
 - Virus, Murine Mammary Tumor, 77-6111
- Pancreatic Neoplasms
 - Serine, Diazoacetate (Ester), 77-6166
- Stomach Neoplasms
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6271
 - Nitrous Acid, 77-6068
- Thyroid Neoplasms
 - Carcinoma, 77-6541
 - Epidemiology, 77-6541
 - Nodule, Solitary, 77-6541
- Virus, Murine Leukemia

- Precancerous Conditions (cont'd)**
 Antigens, Viral, 77-6352
 Thymus Gland, 77-6352
- Prednisolone, Methyl-**
 Bronchial Neoplasms
 Benzo(a)pyrene, 77-6215
 Urea, Methyl Nitroso-, 77-6215
- Prednisone**
 Hepatoma
 Case Report, 77-6246
 Kidney Neoplasms
 Case Report, 77-6246
 Liver Neoplasms
 Histological Study, 77-6513
 Pancreatic Neoplasms
 Case Report, 77-6246
- Pregnancy**
 Carcinogen, Chemical
 Metabolism, 77-6198
 2-Imidazolidinethione
 Half-Life, Blood, 77-6282
 Metabolism, Mouse, Rat, 77-6282
 Liver Neoplasms
 Contraceptives, Oral, 77-6238
 Mammary Neoplasms, Experimental
 Virus, Murine Mammary Tumor, 77-6372
 Virus, Murine Mammary Tumor
 Cell Transformation, Neoplastic, 77-6372
 Virus, Papova
 Urine, 77-6385
 Virus, Polyoma
 Urine, 77-6385
 Virus, Polyoma BK
 Antibodies, Viral, 77-6385
 Virus, Polyoma JC
 Antibodies, Viral, 77-6385
- Premarin**
 Ovarian Neoplasms
 Epidemiology, 77-6228
 Menopause, 77-6228
 4,4-Stilbenediol, α,α' -Diethyl-, 77-6228
- β -Priopiolactone**
 see 2-Oxetanone
- Progesterone**
 Liver Neoplasms
 Diethylamine, *N*-Nitroso-, 77-6236
 Mammary Neoplasms, Experimental
 Dog, Review, 77-6038
 Dose-Response Study, Mouse, 77-6235
 Estrogens, 77-6235
 Neoplasm Transplantation, 77-6203
 Prolactin, 77-6235
 Metabolism
 Review, 77-6037
- Prolactin**
 Breast
 Epidemiology, 77-6233
 Mammary Neoplasms, Experimental
 Dietary Fats, 77-6234
 Neoplasm Transplantation, 77-6203
 Progesterone, 77-6235
- Proline, 4-Hydroxy**
 Sarcoma, Osteogenic
- Proline, 4-Hydroxy (cont'd)**
 Virus, Moloney Murine Sarcoma, 77-6365
- Pronase**
 Lymphoid Tissue
 Rosette Formation, Chick, 77-6472
- Propane, 1,2-Dibromo-3-chloro-**
 Mammary Neoplasms, Experimental
 Carcinoma, 77-6044
 Rat, 77-6044
Salmonella typhimurium
 Mutagenic Activity, 77-6044
 Stomach Neoplasms
 Carcinoma, Epidermoid, 77-6044
 Mouse, 77-6044
 Rat, 77-6044
- Propane, 1,2-Epoxy-3,3,3-trichloro-**
 Benzo(a)pyrene
 DNA, Binding, 77-6204
 Hydro-Lyases, 77-6213
 Metabolism, Rat, 77-6204
 Skin Neoplasms
 Benzo(a)pyrene, 77-6213
- Propane, 1,2,3-Tris(chloromethoxy)-**
 Carcinoma
 Mouse, 77-6045
 Sarcoma
 Mouse, 77-6045
 Skin Neoplasms
 Carcinoma, 77-6045
 Papilloma, 77-6045
- 2-Propanol, 1-(2-Allyloxyphenoxy)-3-(isopropylamino)-**
 Diet
 Carcinogenic Potential, Mouse, 77-6241
 Dose-reponse Study
 Carcinogenic Potential, Mouse, 77-6241
 Liver
 Carcinogenic Potential, Mouse, 77-6241
- 2-Propanol, 1-(*p*-*t*-Butylphenoxy)-**
 Aramite
 Carcinogenic Metabolite, 77-6160
- Propanol, 1,1'-Iminodi-*N*-nitroso-**
 Hepatoma
 Histological Study, Guinea Pig, 77-6265
 Leukemia, Myelocytic
 Histological Study, Guinea Pig, 77-6265
 Liver Neoplasms
 Angiosarcoma, 77-6265
 Carcinogenic Activity, Hamster, 77-6264
 Cholangioma, 77-6264, 77-6265
 Histological Study, Guinea Pig, 77-6265
 Nose Neoplasms
 Carcinogenic Activity, Hamster, 77-6264
 Pancreatic Neoplasms
 Adenoma, 77-6265
 Carcinogenic Activity, Hamster, 77-6264
 Carcinogenic Activity, Rat, 77-6263
 Carcinoma, 77-6265
 Respiratory Tract Neoplasms
 Adenocarcinoma, 77-6263
 Carcinogenic Activity, Rat, 77-6263
 Carcinoma, Epidermoid, 77-6263
 Thyroid Neoplasms
 Carcinogenic Activity, Rat, 77-6263

- 1-Propanone, 2-Methyl-1,2-di-3-pyridyl-, Tartrate**
 Dimethylamine, *N*-Nitroso-
 Alkylation and Demethylation, 77-6258
 Barbituric Acid, 5-Ethyl-5-phenyl-, 77-6258
 Valeric Acid, 2,2-Diphenyl-, 2-(Diethylamino)ethyl
 Ester Hydrochl, 77-6258
- Propionamide, *N*-Methyl-*N*-nitroso-**
 Cysteine
 Carcinogenic Activity, Nitrosamides, 77-6284
- β -Propiolactone**
 see 2-Oxetanone
- Prostatic Neoplasms**
 Adenocarcinoma
 Histological Study, 77-6112
 Rat, 77-6112
 Biogenic Amines
 Castration, 77-6247
 Metabolism, 77-6247
 Carcinoma, Epidermoid
 Catechol Methyltransferase, 77-6247
 Cholanthrene, 3-Methyl-, 77-6247
 Hydroxyindoleacetic Acid, 77-6247
 Monoamine Oxidase, 77-6247
 Norepinephrine, 77-6247
 Pyrocatechol, 4-(2-Aminoethyl)-, 77-6247
 Serotonin, 77-6247
 Tyrosine Hydroxylase, 77-6247
 Carcinoma, Transitional Cell
 Case Report, 77-6533
 Diagnosis and Prognosis, 77-6533
 Cholanthrene, 3-Methyl-
 Biogenic Amines, 77-6247
 Diet
 Epidemiology, 77-6123
 Testosterone
 Metabolism, 77-6112
- Proteins**
 Adenosine Cyclic 3',5' Monophosphate
 Degradation, Intracellular, 77-6588
 Cell Transformation, Neoplastic
 Cell Membrane, 77-6313
 Contact Inhibition
 Degradation, Intracellular, 77-6588
 Cycloheximide
 Degradation, Intracellular, 77-6588
 Fibroblasts
 Degradation, Intracellular, 77-6588
 Virus, SV40
 Degradation, Intracellular, 77-6588
- Prussian Blue**
 Cesium Radioisotopes
 Cell Transformation, Neoplastic, 77-6299
 Strontium Radioisotopes
 Cell Transformation, Neoplastic, 77-6299
- Psoriasis**
 Carcinoma, Epidermoid
 Case Report, 77-6522
 Skin Neoplasms
 Carcinoma, Epidermoid, 77-6522
- Purine, 2-Amino-6-methoxy-**
 Urea, Methyl Nitroso-
 Brain, Rat, 77-6276
 DNA, 77-6276
- Purine-6-thiol**
 Alanine, 3-(*p*-(Bis(2-chloroethyl)amino)phenyl)-
 Antineoplastic Agents, 77-6295
 Antineoplastic Agents
 Carcinogenic Activity, Mouse, 77-6295
 DNA Repair
 Spleen, Rat, 77-6293
 Streptozotocin
 Antineoplastic Agents, 77-6295
 Ultraviolet Rays
 DNA Repair, 77-6293
- Pyrene**
 Neoplasms
 Epidemiology, 77-6200
- 3,6-Pyridazinedione, 1,2-Dihydro-**
 Hydrazine, 1,1-Dimethyl-
 Tobacco, 77-6184
- 5*H*-Pyrido(4,3-*b*)indole, 3-Amino-1-methyl-**
 Tryptophan
 Pyrolysate, Mutagenic Metabolite, 77-6141
- Pyrocatechol**
 Skin Neoplasms
 Carcinoma, Epidermoid, 77-6042
 Papilloma, 77-6042
- Pyrocatechol, 4-(2-Aminoethyl)-**
 Prostatic Neoplasms
 Carcinoma, Epidermoid, 77-6247
- Pyrrolidine, 1-Nitroso-**
 Food Contamination
 Carcinogen, Environmental, 77-6065
- Pyruvate Kinase**
 Hepatoma
 Case Report, Minimal Deviation Tumor, 77-6514
 Isoenzymes, 77-6514
- Quinoline, 4-Nitro-, 1-Oxide**
 Chromosome Aberrations
 Xeroderma Pigmentosum, 77-6287
 DNA Repair
 Xeroderma Pigmentosum, 77-6287
 Guanyl Cyclase
 Colon, Liver, Rat, 77-6273
 Urea, Hydroxy-
 Cell Transformation, Neoplastic, 77-6288
 DNA Repair, 77-6288
- 8-Quinolinol, Copper (II) Chelate**
 Sarcoma, Reticulum Cell
 Mouse, 77-6056
- Radiation**
 Leukemia
 Occupational Hazard, Review, 77-6081
 Nuclear Reactors
 Epidemiology, Review, 77-6081
- Radiation, Ionizing**
 Benzene
 Epidemiology, 77-6125
 Bone Neoplasms
 Rat, 77-6301
 Sarcoma, Osteogenic, 77-6301
 Breast Neoplasms
 Carcinoma, 77-6084
 Epidemiology, 77-6083, 77-6116
 Cells, Cultured

Radiation, Ionizing (cont'd)

- Cell Cycle Kinetics, 77-6304
- Chromosome Aberrations
 - Lymphocytes, 77-6078
- DNA Replication
 - Cells, Cultured, 77-6304
- Dose-Response Study
 - Epidemiology, 77-6083
 - Models, Theoretical, 77-6082
- Fibrosarcoma
 - Transplantation Immunology, 77-6444
- Head and Neck Neoplasms
 - Review, 77-6080
- Hepatoma
 - Aniline, *N,N*-Dimethyl-*p*-phenylazo-, 77-6456
 - Transplantation Immunology, 77-6456
- Leukemia
 - Dose-Response Study, 77-6082
 - Epidemiology, 77-6079, 77-6083, 77-6125
 - Epidemiology, Review, 77-6104
- Models, Mathematical
 - Epidemiology, 77-6302
- Neoplasms
 - Epidemiology, 77-6084
- Neoplasms, Experimental
 - Neoplasm Metastasis, 77-6447
- Ovarian Neoplasms
 - Virus-Like Particles, 77-6342
- Salivary Gland Neoplasms
 - Review, 77-6080
- Skin Neoplasms
 - Rat, 77-6305
 - Review, 77-6080
- Thyroid Neoplasms
 - Carcinoma, 77-6083
 - Radium, 77-6077
 - Review, 77-6080
- Urea, Ethyl Nitroso-
 - Transplacental Carcinogenesis, 77-6280

Radiation, Non-Ionizing

- Salmonella typhimurium*
 - Mutagenic Activity, 77-6306

Radium

- Occupational Hazard
 - Epidemiology, 77-6300
- Thyroid Neoplasms
 - Radiation, Ionizing, 77-6077

Rectal Neoplasms

- Coal
 - Epidemiology, 77-6582
- Diet
 - Epidemiology, 77-6123, 77-6569

Resorcinol

- Liver Neoplasms
 - Hemangioma, 77-6042
- Lung Neoplasms
 - Adenoma, 77-6042
- Lymphoma
 - Mouse, 77-6042

Respiratory System

- Carcinogen, Environmental
 - Immune Response, Review, 77-6017

Respiratory Tract Neoplasms

- Acrolein

Respiratory Tract Neoplasms (cont'd)

- Hamster, 77-6214
- Adenocarcinoma
 - Ethenamine, *N*-Ethylene-*N*-nitroso-, 77-6248
 - 2-Propanol, 1,1'-Iminodi-*N*-nitroso-, 77-6263
- Antigens, Neoplasm
 - Benzo(a)anthracene, 7,12-Dimethyl-, 77-6492
 - Benzo(a)pyrene, 77-6492
 - Cholanthrene, 3-Methyl-, 77-6492
- Benzo(a)pyrene
 - Dose-Response Study, Hamster, 77-6211
 - Hamster, 77-6214
 - Solvents, 77-6211
- Carbamic Acid, Ethyl Ester
 - Ultrastructural Study, Hamster, 77-6267
- Carcinoma, Epidermoid
 - Antigens, Neoplasm, 77-6492
 - 2-Propanol, 1,1'-Iminodi-*N*-nitroso-, 77-6263
 - Rat, 77-6492
- Diethylamine, *N*-Nitroso-
 - Hamster, 77-6214
 - Ultrastructural Study, Hamster, 77-6267
- Dimethylamine, *N*-Nitroso-
 - Carcinogenic Activity, 77-6069
 - Ultrastructural Study, Hamster, 77-6267
- Ethenamine, *N*-Ethylene-*N*-nitroso-
 - Carcinoma, Epidermoid, 77-6248
 - Neoplasm Metastasis, 77-6248
 - Ultrastructural Study, Hamster, 77-6267
- Genetics
 - Epidemiology, 77-6571
- Isopropyl Alcohol
 - Epidemiology, 77-6054
- 2-Propanol, 1,1'-Iminodi-*N*-nitroso-
 - Carcinogenic Activity, Rat, 77-6263
- Urea, Ethyl Nitroso-
 - Ultrastructural Study, Hamster, 77-6267

Reticulosarcoma

- see Sarcoma, Reticulum Cell

Retinoblastoma

- Chromosome Aberrations
 - Epidemiology, 77-6552
- Neoplasms, Multiple Primary
 - Case Report, 77-6551
 - Genetics, 77-6551

13-cis-Retinoic Acid

- Bladder Neoplasms
 - 1-Butanol, 4-(Butylnitrosamino)-, 77-6260

Retinol

- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Guanyl Cyclase, 77-6273

Retinol Acetate

- Abnormalities
 - Vagina, Mouse, 77-6230
- Benzo(a)pyrene
 - Aryl Hydrocarbon Hydroxylases, 77-6212
- Estradiol
 - Vagina, Mouse, 77-6230

Reverse Transcriptase

- Bacteriophages
 - RNA Replication, 77-6320
- Interferon
 - Virus, Murine Mammary Tumor, 77-6375
- RNA, Transfer
 - Enzymatic Activity, 77-6323

Reverse Transcriptase (cont'd)

- Virus, Avian Myeloblastosis
 - Antigens, Viral, 77-6324
 - DNA Replication, 77-6321
 - Enzymatic Activity, 77-6323
 - Isolation and Characterization, 77-6321
 - RNA, Viral, 77-6320
- Virus, DNA Tumor
 - Cell Transformation, Neoplastic, Review, 77-6085
- Virus, Kirsten Murine Sarcoma
 - Dexamethasone, 77-6370
 - Interferon, 77-6370
 - Uridine, 2'-Deoxy-5-iodo-, 77-6370
- Virus-Like Particles
 - Cells, Cultured, 77-6339
- Virus, Moloney Murine Leukemia
 - Enzymatic Activity, 77-6323
- Virus, Murine Mammary Tumor
 - Isolation and Characterization, 77-6373
- Virus, Rauscher Murine Leukemia
 - Streptovaricins, 77-6359
- Virus, RNA Tumor
 - Cell Transformation, Neoplastic, Review, 77-6085
- Virus, Rous Sarcoma
 - Enzymatic Activity, 77-6323

Ribonucleotides

- Ethylene, Chloro-
- Nucleic Acids, 77-6157

RNA

- Cytoplasm
 - Liver Regeneration, 77-6593
- Liver Regeneration
 - DNA-RNA Hybridization, 77-6593
- Polyribosomes
 - Liver Regeneration, 77-6593
- Viral Proteins
 - Binding, 77-6366
- Virus, SV40
 - Uracil Nucleotides, 77-6432
 - Uridine Incorporation, 77-6432
 - Virus Replication, 77-6432

RNA, Messenger

- DNA-RNA Hybridization
 - Ultrastructural Study, 77-6392
- Histones
 - Isolation and Characterization, 77-6594
- Virus, Adeno 2
 - DNA, Viral, 77-6392
- Virus, Rous Sarcoma
 - Cell Transformation, Neoplastic, 77-6313
- Virus, SV40
 - Base Sequence, 77-6417
 - Viral Proteins, 77-6417

RNA Polymerase

- Acetamide, Thio-
 - Chromatin, Binding, 77-6132
 - Liver, Rat, 77-6132
- Cadmium
 - Carcinogenic Potential, 77-6217
- Cobalt
 - Carcinogenic Potential, 77-6217
- Copper
 - Carcinogenic Potential, 77-6217
- Lead
 - Carcinogenic Potential, 77-6217
- Manganese

RNA Polymerase (cont'd)

- Carcinogenic Potential, 77-6217

Metals

- Carcinogen, Environmental, 77-6217
- Mutagenic Activity, 77-6217

Virus-Like Particles

- Enzymatic Activity, 77-6347

Virus, SV40

- DNA, Viral, 77-6425
- RNA, Viral, 77-6425

RNA Replication**Bacteriophages**

- Reverse Transcriptase, 77-6320

Virus, Harvey Murine Sarcoma

- Stress, Anaerobic, 77-6367

Virus, Kirsten Murine Sarcoma

- Stress, Anaerobic, 77-6367

Virus, Murine Leukemia

- Cycloheximide, 77-6367
- Stress, Anaerobic, 77-6367
- Uridine, 5-Bromo-2'-deoxy-, 77-6367

Virus, Murine Sarcoma

- Cycloheximide, 77-6367
- Uridine, 5-Bromo-2'-deoxy-, 77-6367

Virus, Polyoma

- DNA, Viral, 77-6380
- Temperature Sensitive Mutants, 77-6377

RNA, Transfer

- Butyric Acid, 2-Amino-4-(ethylthio)-
 - Metabolism, Rat, 77-6164
- Reverse Transcriptase
 - Enzymatic Activity, 77-6323

RNA, Viral**Bacteriophages**

- Poly A, 77-6320

Plasmacytoma

- Virus-Like Particles, 77-6348

Virus, Avian Leukosis

- Cell Transformation, Neoplastic, 77-6330

Virus, Avian Myeloblastosis

- Base Sequence, 77-6322
- Viral Proteins, 77-6319
- Virus Replication, 77-6322
- Reverse Transcriptase, 77-6320

Virus, Avian RNA Tumor

- Isolation and Characterization, 77-6330

Virus, Avian Sarcoma

- Cell Transformation, Neoplastic, 77-6330

- Cells, Cultured, 77-6311

- Isolation and Characterization, 77-6311

Virus, Moloney Murine Leukemia

- Virus, Moloney Murine Sarcoma, 77-6364

Virus, Murine Leukemia

- Isolation and Characterization, 77-6344

Virus, Murine Mammary Tumor

- Isolation and Characterization, 77-6374

Virus, Polyoma

- DNA-RNA Hybridization, 77-6379
- Temperature Sensitive Mutants, 77-6377

Virus, Rous-Associated

- Cells, Cultured, 77-6316

Virus, Rous Sarcoma

- Cells, Cultured, 77-6316

- Viral Proteins, 77-6314

Virus, SV40

- Isolation and Characterization, 77-6425
- RNA Polymerase, 77-6425

- RNA, Viral (cont'd)**
 Temperature Sensitive Mutants, 77-6420
 Virus, Visna
 Isolation and Characterization, 77-6333
 Virus Replication, 77-6333
- Rubber**
 Bladder Neoplasms
 Epidemiology, 77-6583
- Rubratoxin B**
 Toxicology
 Dog, 77-6175
- Safrole**
 see Benzene, 4-Allyl-1,2-(methylenedioxy)-
- Salicylamide**
 Benzo(a)pyrene
 DNA, Binding, 77-6204
 Metabolism, Rat, 77-6204
- Salivary Gland Neoplasms**
 Radiation, Ionizing
 Review, 77-6080
- Salmonella typhimurium**
 Air Pollutants
 Mutagenic Activity, 77-6199
 Anisole, *p*-Allyl-
 Mutagenic Activity, 77-6146
 2-Anthracenamide
 Mutagenic Activity, 77-6198
 Benz(a)anthracene, 7,12-Dimethyl-
 Mutagenic Activity, 77-6198
 Benzene, 4-Allyl-1,2-(methylenedioxy)-
 Mutagenic Activity, 77-6146
 Benzo(a)pyrene
 Mutagenic Activity, 77-6061, 77-6198
 Mutagenic Activity, Diol Epoxides, 77-6209
 Bile Acids and Salts
 Mutagenic Activity, 77-6297
 2-Butene, 1,4-Dichloro-
 Mutagenic Activity, 77-6046
 Cholanthrene, 3-Methyl-
 Mutagenic Activity, 77-6198
 Chrysene
 Mutagenic Activity, 77-6202
 Chrysene, 1,2-Dihydro-1,2-dihydroxy-
 Mutagenic Activity, 77-6202
 Chrysene, 3,4-Dihydro-3,4-dihydroxy-
 Mutagenic Activity, 77-6202
 Chrysene, 5,6-Dihydro-1,2-dihydroxy-
 Mutagenic Activity, 77-6202
 Ethane, 1,2-Dibromo-
 Mutagenic Activity, 77-6041
 Ethylene, Chloro-
 Mutagenic Activity, 77-6039
 Ethylene, 1,1-Dichloro-
 Mutagenic Activity, 77-6039
 Ethylene, Trichloro-
 Mutagenic Activity, 77-6039
 Lithocholic Acid
 Mutagenic Activity, 77-6297
 Neutral Red
 Mutagenic Activity, 77-6306
 Petroleum
 Mutagenic Activity, 77-6296
 Phenol, 2-Methoxy-4-(2-propenyl)-
 Mutagenic Activity, 77-6146
- Salmonella typhimurium (cont'd)**
 Propane, 1,2-Dibromo-3-chloro-
 Mutagenic Activity, 77-6044
 Radiation, Non-Ionizing
 Mutagenic Activity, 77-6306
 Smoking
 Mutagenic Activity, 77-6198
 Succinic Anhydride
 Mutagenic Activity, 77-6057
- Sarcoidosis**
 T-Lymphocytes
 Immune Response, 77-6446
- Sarcoma**
 Antigenic Determinants
 Transplantation Immunology, 77-6493
 Antigens, Neoplasm
 Antigenic Determinants, 77-6493
 Isolation and Characterization, 77-6490
- BCG**
 T-Lymphocytes, 77-6445
 Transplantation Immunology, 77-6445
 Benzene, 1,4-Bis(chloromethoxymethyl)-
 Mouse, 77-6043
 Benzo(a)pyrene
 BCG, 77-6445
 Rat, 77-6210
 2-Butene, 1,4-Dichloro-
 Mouse, 77-6046
 Cells, Cultured
 Cytotoxicity Tests, Immunologic, 77-6437
 Cholanthrene, 3-Methyl-
 Antigenic Determinants, 77-6493
 Antigens, Neoplasm, 77-6490
 T-Lymphocytes, 77-6451
 Transplantation Immunology, 77-6451
 Ethane, 1,2-Bis(chloromethoxy)-
 Mouse, 77-6047
 Fluorescein, 2',4',5',7'-Tetrabromo-, Disodium Salt
 Liver Neoplasms, 77-6055
 Head and Neck Neoplasms
 Neoplasm Metastasis, 77-6549
 Histocompatibility Antigens
 Transplantation Immunology, 77-6493
 Immunity, Cellular
 Neoplasm Metastasis, 77-6451
 Mammary Neoplasms, Experimental
 Dog, Review, 77-6038
 Polylysine
 Mouse, 77-6600
 Propane, 1,2,3-Tris(chloromethoxy)-
 Mouse, 77-6045
 Succinic Anhydride
 Rat, 77-6057
 Transplantation Immunology
 Neoplasm Metastasis, 77-6451
- Sarcoma, Ewing's**
 Ultrastructural Study
 Histological Study, 77-6498
- Sarcoma, Osteogenic**
 Bone Neoplasms
 Radiation, Ionizing, 77-6301
 Virus, Moloney Murine Sarcoma
 Alkaline Phosphatase, 77-6365
 Histological Study, 77-6365
 Hypercalcemia, 77-6365

Sarcoma, Osteogenic (cont'd)
Proline, 4-Hydroxy, 77-6365
Ultrastructural Study, 77-6365

Sarcoma, Reticulum Cell
Acetamide, *N*-Fluorenyl-2-yl-
Mouse, 77-6135
Acetic Acid, 2,4-Dichlorophenoxy-
Mouse, 77-6052
B-Lymphocytes
Mouse, 77-6468
Lymphoma
Epidemiology, 77-6125
8-Quinololinol, Copper (II) Chelate
Mouse, 77-6056

Schistosoma mansoni
B-Lymphocytes
DNA Replication, 77-6469
T-Lymphocytes
DNA Replication, 77-6469

Schistosomiasis
Bladder Neoplasms
Nitrosamines, 77-6266

Selenium
Animals, Laboratory
Toxicology, Review, 77-6076
Occupational Hazard
Toxicology, Review, 77-6076

Seminoma
see Disgerminoma

Serine, Diazoacetate (Ester)
DNA Repair
Dose-Response Study, 77-6167
Kidney, Liver, Pancreas, Rat, 77-6167
Pancreatic Neoplasms
Animal Model, Rat, 77-6166
Dose-Response Study, 77-6166
Precancerous Conditions, 77-6166
Species Difference, 77-6166

Serotonin
Prostatic Neoplasms
Carcinoma, Epidermoid, 77-6247

Sertoli Cell Tumor
Fish
Histological Study, 77-6537
Fishes
Ultrastructural Study, 77-6537

Silica
Fibrosarcoma
Transplantation Immunology, 77-6444

Silica, Crystalline
BCG
Immunity, Cellular, 77-6461
Corynebacterium parvum
Immunity, Cellular, 77-6461

Silver
Carcinogenic Activity
Rat, 77-6220

Skin
Benzene
Ultrastructural Study, Mouse, 77-6144

Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
Carcinogenic Activity, Review, 77-6010
Benzo(a)pyrene
Carcinogenic Activity, Review, 77-6010
Propane, 1,2-Epoxy-3,3,3-trichloro-, 77-6213
4-Biphenylamine
Rat, 77-6286
2-Butene, 1,4-Dichloro-
Carcinoma, Epidermoid, 77-6046
Papilloma, 77-6046
Carcinogen, Environmental
Co-carcinogenic Activity, Review, 77-6010
Carcinoma
p-Benzoquinone, 77-6049
Propane, 1,2,3-Tris(chloromethoxy)-, 77-6045
Carcinoma, Epidermoid
Benzo(a)pyrene, 77-6042
Models, Biological, 77-6517
Psoriasis, 77-6522
Pyrocatechol, 77-6042
Cylindroma
Ultrastructural Study, 77-6523
Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
Carcinogenic Potential, Rat, 77-6156
Fish
Epidemiology, 77-6586
Genetics
Epidemiology, 77-6571
Hydroxylamine, *N*-1-Naphthyl-
Rat, 77-6286
1-Naphthylamine
Rat, 77-6286
2-Naphthylamine
Rat, 77-6286
Papilloma
Benzene, 1,4-Bis(chloromethoxymethyl)-, 77-6043
Benzo(a)pyrene, 77-6042
p-Benzoquinone, 77-6049
Ethane, 1,2-Bis(chloromethoxy)-, 77-6047
Fish, 77-6586
Propane, 1,2,3-Tris(chloromethoxy)-, 77-6045
Pyrocatechol, 77-6042
Radiation, Ionizing
Rat, 77-6305
Review, 77-6080
Ultraviolet Rays
Epidemiology, Review, 77-6124
Smoking
Aryl Hydrocarbon Hydroxylases
Enzymatic Activity, Hamster, Rat, 77-6194
Bladder Neoplasms
Epidemiology, 77-6059
Bronchi
Macrophages, 77-6511
Carcinogen, Environmental
Co-carcinogenic Effect, Review, 77-6017
Carcinogenic Potential
Mouse, 77-6186
Carcinoma, Bronchogenic
Carcinogen, Environmental, 77-6019
Cell Differentiation
Tobacco Supplement, 77-6187
Trachea, Rat, 77-6187
Cervix Neoplasms
Carcinoma, Epidermoid, 77-6072
Epidemiology, 77-6072

Smoking (cont'd)

- Models, Theoretical, 77-6072
- Esophageal Neoplasms
 - Epidemiology, 77-6123
- Ether, Chloromethyl Methyl
 - Co-carcinogenic Effect, 77-6071
- Hemoglobins
 - Dose-Response Study, Mouse, 77-6191
- Laryngeal Neoplasms
 - Epidemiology, 77-6123
 - Hyperplasia, 77-6188
 - Metaplasia, 77-6188
 - Mouse, 77-6243
 - Precancerous Conditions, 77-6188
 - Ultrastructural Study, Rat, 77-6188
- Lung Neoplasms
 - Adenoma, 77-6189
 - Diet, Review, 77-6127
 - Dose-Response Study, 77-6250
 - Epidemiology, 77-6123
 - Epidemiology, Review, 77-6124, 77-6127
 - Ether, Chloromethyl Methyl, 77-6071
 - Genetics, Review, 77-6127
 - Macrophages, 77-6189
 - Papilloma, 77-6189
 - Precancerous Conditions, 77-6189, 77-6510
 - Transplantation, Heterologous, 77-6510
 - Ultrastructural Study, Hamster, 77-6189
- Lymphocytes
 - Aryl Hydrocarbon Hydroxylases, 77-6193
- Macrophages, 77-6511
 - Agglutination, 77-6192
 - Aryl Hydrocarbon Hydroxylases, 77-6192, 77-6193
 - Cell Survival, 77-6187
 - Cellular Inclusions, 77-6192
 - Concanavalin A, 77-6192
 - Immunity, Cellular, 77-6192
 - Ultrastructural Study, 77-6192, 77-6511
- Mouth Neoplasms
 - Diagnosis and Prognosis, 77-6183
 - Epidemiology, 77-6123
- Pharyngeal Neoplasms
 - Epidemiology, 77-6123
- Salmonella typhimurium*
 - Mutagenic Activity, 77-6198
- Tobacco Supplement
 - Mucociliary Activity, 77-6187
- Total Particulate Matter
 - Respiratory System, Rat, 77-6191
- Toxicology
 - Rat, 77-6190
- Trachea
 - Glycoproteins, 77-6070
 - Goblet Cells, 77-6070
 - Mucus, 77-6070

Sodium Oxide

- Plutonium Oxide
 - Lung, 77-6224

Somatotropin

- Hepatoma
 - Aflatoxin B1, 77-6174

Spermatozoa

- Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
 - Bone Marrow Cells, 77-6281
 - Chromosome Aberrations, 77-6281
- Urea, 1-(2-Chloroethyl)-3-(2-hydroxyethyl)-1-nitroso-

Spermatozoa (cont'd)

- Chromosome Aberrations, 77-6281

Statolon

- Erythroleukemia
 - Virus, Friend Murine Leukemia, 77-6356

Stearic Acid, 12-Hydroxy-

- Carcinogen, Chemical
 - Oxidative Phosphorylation, 77-6165

Stearic Acid, 12-Hydroxy-, Methyl Ester

- Carcinogen, Chemical
 - Oxidative Phosphorylation, 77-6165

Steroids

- Metabolism
 - Review, 77-6037

4,4'-Stilbenediol, α,α' -Diethyl-

- Cervix Neoplasms
 - Carcinoma, Epidermoid, 77-6029
 - Review, 77-6029
- Contraceptives, Oral
 - Teratogenic Activity, 77-6028
- Gynecologic Neoplasms
 - Adenocarcinoma, 77-6229
 - Strain Difference, Mouse, 77-6229
- Mammary Neoplasms, Experimental
 - Strain Difference, Mouse, 77-6229
- Metabolism
 - Chimpanzee, 77-6227
 - Monkey, 77-6227
- Ovarian Neoplasms
 - Epidemiology, 77-6228
 - Menopause, 77-6228
 - Premarin, 77-6228
- Strain Difference
 - Ultrastructural Study, Mouse, 77-6229
- Transplacental Carcinogenesis
 - Review, 77-6034
- Uterine Neoplasms
 - Review, 77-6034
- Vaginal Neoplasms
 - Adenocarcinoma, 77-6113
 - Transplacental Carcinogenesis, 77-6113

Stomach Neoplasms

- Adenoma
 - Histological Study, 77-6500
- Ascorbic Acid
 - Nitrosamines, 77-6064
- Carcinoma
 - Diagnosis and Prognosis, 77-6507
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6271
 - Histological Study, 77-6499, 77-6500
 - Ulcer, 77-6501
 - Ultrastructural Study, 77-6499
- Carcinoma, Epidermoid
 - Ethane, 1,2-Dibromo-, 77-6041
- Diet
 - Epidemiology, 77-6123, 77-6569
- Dimethylamine, *N*-Nitroso-
 - Epidemiology, 77-6064
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Precancerous Conditions, 77-6271
 - Ultrastructural Study, Rat, 77-6271
- Histological Study
 - Immune Response, 77-6098
- Hyperplasia

- Stomach Neoplasms (cont'd)**
 Polychlorobiphenyl Compounds, 77-6149
 Nitrous Acid
 Epidemiology, 77-6068
 Precancerous Conditions, 77-6068
 Water Pollution, 77-6068
 Peptic Ulcer
 Pathology, 77-6110
 Propane, 1,2-Dibromo-3-chloro-
 Carcinoma, Epidermoid, 77-6044
 Mouse, 77-6044
 Rat, 77-6044
- Streptovaricins**
 Virus, Rauscher Murine Leukemia
 Reverse Transcriptase, 77-6359
- Streptozotocin**
 Antineoplastic Agents
 6-Mercaptopurine, 77-6295
- Strontium Radioisotopes**
 Alginic Acid, Sodium Salt
 Cell Transformation, Neoplastic, 77-6299
 Bone Neoplasms
 Radiation-Protective Agents, 77-6299
 Calcium, 77-6299
 Prussian Blue
 Cell Transformation, Neoplastic, 77-6299
- Succinic Acid, Mono(2,2-dimethylhydrazide)**
 Angiosarcoma
 Mouse, 77-6168
 Hemangioma
 Mouse, 77-6168
 Kidney Neoplasms
 Adenoma, 77-6168
 Mouse, 77-6168
 Lung Neoplasms
 Adenocarcinoma, 77-6168
 Adenoma, 77-6168
 Mouse, 77-6168
- Succinic Anhydride**
Salmonella typhimurium
 Mutagenic Activity, 77-6057
 Sarcoma
 Rat, 77-6057
- Surface Properties**
 Burkitt's Lymphoma
 B-Lymphocytes, 77-6565
 Hodgkin's Disease
 Cell Membrane, 77-6565
 B-Lymphocytes, 77-6565
 Infectious Mononucleosis
 Cell Membrane, 77-6565
 B-Lymphocytes, 77-6565
 Leukemia, Lymphoblastic
 Cell Membrane, 77-6565
 T-Lymphocytes, 77-6565
- Sweat Gland Neoplasms**
 Carcinoma, Epidermoid
 Case Report, 77-6520
 Neoplasm Metastasis, 77-6520
- 2,4,5,-T**
 see Acetic Acid, (2,4,5-Trichlorophenoxy)-
- Tars**
 Lymphocytes
- Tars (cont'd)**
 Aryl Hydrocarbon Hydroxylases, 77-6193
 Macrophages
 Aryl Hydrocarbon Hydroxylases, 77-6193
- Tellurium**
 Animals, Laboratory
 Toxicology, Review, 77-6076
 Occupational Hazard
 Toxicology, Review, 77-6076
- Teratoid Tumor**
 Ovarian Neoplasms
 Histological Study, Fish, 77-6526
 Virus, SV40
 Cell Differentiation, 77-6431
 Cell Transformation, Neoplastic, 77-6431
 Creatine Kinase, 77-6431
 Plasminogen, 77-6431
- Teratoma**
 see Teratoid Tumor
- Testicular Neoplasms**
 Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 Carcinogenic Potential, Rat, 77-6156
- Testosterone**
 Hepatoma
 Case Report, 77-6246
 Kidney Neoplasms
 Case Report, 77-6246
 Laryngeal Neoplasms
 Histological Study, 77-6243
 Liver Neoplasms
 Histological Study, 77-6513
 B-Lymphocytes
 Cell Differentiation, 77-6452
 Chick Embryo, 77-6452
 Pancreatic Neoplasms
 Case Report, 77-6246
 Prostatic Neoplasms
 Metabolism, 77-6112
- Testosterone, Propionate**
 Gynecologic Neoplasms
 Dose-Response Study, 77-6245
 Histological Study, Mouse, 77-6245
 Precancerous Conditions, 77-6245
 Transplacental Carcinogenesis, Mouse, 77-6245
- 12-O-Tetradecanoylphorbol-13-acetate**
 Benz(a)anthracene, 7,12-Dimethyl-
 Co-carcinogenic Activity, Review, 77-6010
- Thymidine Kinase**
 Virus, Herpes Simplex 2
 Cells, Cultured, 77-6402
 Chromosomes, 77-6402
 Enzymatic Activity, 77-6402
- Thymus Gland**
 Neoplasms, Experimental
 Neoplasm Metastasis, 77-6447
 Virus, Murine Leukemia
 Antigens, Viral, 77-6352
 Precancerous Conditions, 77-6352
- Thyroid Gland**
 2-Imidazolidinethione
 Histological Study, Hamster, Rat, 77-6283

- Thyroid Neoplasms**
 Adenocarcinoma
 Neoplasms, Multiple Primary, 77-6543
 Adenoma
 Isopropyl Oils, 77-6054
 Biphenyl, Octabromo-
 Precancerous Conditions, Review, 77-6015
 Carcinoma
 Amyloidosis, 77-6542
 Enzymatic Activity, 77-6542
 Epidemiology, 77-6540
 Histological Study, 77-6540
 Precancerous Conditions, 77-6541
 Radiation, Ionizing, 77-6083
 Ultrastructural Study, 77-6542
 Carcinoma, Papillary
 Neoplasms, Multiple Primary, 77-6543
 Fish
 Histological Study, 77-6538
 Goiter
 Neoplasms, Multiple Primary, 77-6543
 2-Imidazolidinethione
 Rat, 77-6283
 Iodine Radioisotopes
 Thyroxine, 77-6226
 Uracil, 6-Propyl-2-thio-, 77-6226
 Nervous System Neoplasms
 Brachial Plexus, 77-6543
 Case Report, 77-6543
 Neoplasms, Multiple Primary, 77-6543
 Neurilemmoma
 Case Report, 77-6543
 Neurofibroma
 Case Report, 77-6543
 Precancerous Conditions
 Epidemiology, 77-6541
 Nodule, Solitary, 77-6541
 2-Propanol, 1,1'-Iminodi-*N*-nitroso-
 Carcinogenic Activity, Rat, 77-6263
 Radiation, Ionizing
 Review, 77-6080
 Radium
 Radiation, Ionizing, 77-6077
 Thyroid Neoplasms
 1-Imidazolidinethione, 77-6283
 Thyrotropin
 Serum Levels, 77-6226
 Uracil, 6-Propyl-2-thio-
 Thyroxine, 77-6226
- Thyrotropin**
 Thyroid Neoplasms
 Serum Levels, 77-6226
- Thyroxine**
 Thyroid Neoplasms
 Iodine Radioisotopes, 77-6226
 Uracil, 6-Propyl-2-thio-, 77-6226
- Tobacco**
 Ethanol, 2,2'-(Phenylamino)di-, *N*-Nitroso-
 Concentration Levels, 77-6184
 Hydrazine, 1,1-Dimethyl-
 Concentration Levels, 77-6184
 3,6-Pyridazinedione, 1,2-Dihydro-, 77-6184
 Mouth Neoplasms
 Epidemiology, Review, 77-6124
 Nicotine, 1'-Nitroso-1'-demethyl-
 Quantitation Method, 77-6185
- p*-Toluamide, *N*-Isopropyl- α -(2-methylhydrazino)-, HCl**
 Antineoplastic Agents
 Carcinogenic Activity, Mouse, 77-6295
- o*-Toluidine, 4-(*o*-Tolylazo)-**
 Cell Transformation, Neoplastic
 Dose-Response Study, 77-6013
- Toxoplasma gondii***
 Cervix Uteri
 Case Report, 77-6074
 Erythrocytes
 Endocytosis, 77-6462
 Hemoglobins
 Endocytosis, 77-6462
 Macrophages
 Endocytosis, 77-6462
- Trace Elements**
 Benzo(a)pyrene
 Aryl Hydrocarbon Hydroxylases, 77-6216
 Co-carcinogenic Effect, 77-6216
 Liposarcoma
Perodicticus potto, 77-6152
- Trachea**
 Benzyl Alcohol, 3,4-Dihydroxy-
 2-((isopropylamino)methyl)-
 Glycoproteins, 77-6070
 Goblet Cells, 77-6070
 Mucus, 77-6070
 Smoking
 Glycoproteins, 77-6070
 Goblet Cells, 77-6070
 Mucus, 77-6070
- Transferases**
 Benzene, (Epoxyethyl)-
 Metabolism, 77-6158
- Transplantation, Heterologous**
 Colonic Neoplasms
 Adenocarcinoma, 77-6503
 Carcinoembryonic Antigen, 77-6503
 Cell Differentiation, 77-6503
 Phenotype, 77-6503
 Lung Neoplasms
 Neurilemmoma, 77-6544
 Precancerous Conditions, 77-6510
 Smoking, 77-6510
 Ultrastructural Study, 77-6510
- Transplantation, Homologous**
 Hematopoietic Stem Cells
 Chick Embryo, 77-6452
 Mammary Neoplasms, Experimental
 Ovary, 77-6232
- Transplantation Immunology**
 Adenocarcinoma
 Carrageen, 77-6460
 BCG
 T-Lymphocytes, 77-6445
 Fibrosarcoma
 Benz(a)anthracene, 7,12-Dimethyl-, 77-6444
Corynebacterium parvum, 77-6444
 Hypersensitivity, Delayed, 77-6444
 T-Lymphocytes, 77-6444
 Monocytes, 77-6444
Mycobacterium bovis, 77-6444
 Radiation, Ionizing, 77-6444

Transplantation Immunology (cont'd)

Silica, 77-6444
Trypan Blue, 77-6444

Hepatoma

Antigens, Neoplasm, 77-6456
Radiation, Ionizing, 77-6456

Histocompatibility Antigens

Cholanthrene, 3-Methyl-, 77-6448

Lung Neoplasms

T-Lymphocytes, 77-6442

Lymphoma

Cholanthrene, 3-Methyl-, 77-6455
Immune Serums, 77-6458
Mitomycin C, 77-6455
Viral Vaccines, 77-6458
Virus, Murine Leukemia, 77-6458

Neoplasms, Experimental

Benz(a)anthracene, 7,12-Dimethyl-, 77-6447
Cholanthrene, 3-Methyl-, 77-6448
T-Lymphocytes, 77-6447, 77-6448
Virus, SV40, 77-6448

Sarcoma

Antigenic Determinants, 77-6493
BCG, 77-6445
Histocompatibility Antigens, 77-6493
Neoplasm Metastasis, 77-6451

Virus, Adeno 3

Age Factors, 77-6334

Virus, SV40

Histocompatibility Antigens, 77-6427

1,1,1-Trichloro-2,3-propene Oxide

see Propane, 1,2-Epoxy-3,3,3-trichloro-

Triglycerides

Liposarcoma
Perodicticus potto, 77-6152

Trypan Blue

Fibrosarcoma
Transplantation Immunology, 77-6444

Trypsin

Lymphocytes
Immune Response, 77-6470
Lymphoid Tissue
Rosette Formation, Chick, 77-6472
Melanoma
Glycoproteins, 77-6589

Tryptophan

Bladder Neoplasms
Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
77-6139
Metabolism, 77-6140
5*H*-Pyrido(4,3-*b*)indole, 3-Amino-1-methyl-
Pyrolysate, Mutagenic Metabolite, 77-6141

Tryptophan, 5-Hydroxy-

Bladder Neoplasms
Review, 77-6060

Tyrosine Hydroxylase

Prostatic Neoplasms
Carcinoma, Epidermoid, 77-6247

Ulcer

Stomach Neoplasms
Carcinoma, 77-6501

Ultraviolet Rays

Benz(a)anthracene, 7,12-Dimethyl-
Co-carcinogenic Activity, Review, 77-6010
Carcinoma, Epidermoid
Sheep, 77-6517

Daunomycin

DNA Repair, 77-6293

DNA Repair

Cells, Cultured, 77-6303
Spleen, Rat, 77-6293

Methotrexate

Spleen, Rat, 77-6293

Mitomycin C

DNA Repair, 77-6293

Purine-6-thiol

DNA Repair, 77-6293

Skin Neoplasms

Epidemiology, Review, 77-6124

Uracil, 5-Fluoro-

DNA Repair, 77-6293

Uracil, 5-Fluoro-

DNA Repair
Spleen, Rat, 77-6293
Ultraviolet Rays
DNA Repair, 77-6293

Uracil Nucleotides

Virus, SV40
RNA, 77-6432

Uracil, 6-Propyl-2-thio-

Thyroid Neoplasms
Iodine Radioisotopes, 77-6226
Thyroxine, 77-6226

Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-

Bone Marrow Cells
Spermatozoa, 77-6281
Chromosome Aberrations
Spermatozoa, 77-6281

Urea, 1-Butyl-1-nitroso-

Brain Neoplasms
Transplacental Carcinogenesis, 77-6002

Urea, 1-(2-Chloroethyl)-3-(2-hydroxyethyl)-1-nitroso-

Chromosome Aberrations
Bone Marrow Cells, 77-6281
Spermatozoa, 77-6281

Urea, 1,3-Dimethyl-1-nitroso-

Brain Neoplasms
Histological Study, 77-6002

Urea, Ethyl Nitroso-

Brain Neoplasms
Transplacental Carcinogenesis, 77-6002
Gastrointestinal Neoplasms
Carcinogenic Activity, 77-6069
Kidney Neoplasms
Carcinogenic Activity, 77-6069
Leukemia
Chromosomes, 77-6279
Cytochemical Study, 77-6279
DNA, 77-6279
Neoplasm Transplantation, 77-6279
Ultrastructural Study, 77-6279
Lung Neoplasms
Adenoma, 77-6280
Transplacental Carcinogenesis, 77-6280, 77-6491

Urea, Ethyl Nitroso- (cont'd)

- Metabolism
 - Carcinogenic Activity, 77-6069
 - Mutagenic Activity, 77-6069
- Nervous System Neoplasms
 - Carcinogenic Activity, 77-6069
- Ovarian Neoplasms
 - Transplacental Carcinogenesis, 77-6280
- Radiation, Ionizing
 - Transplacental Carcinogenesis, 77-6280
- Respiratory Tract Neoplasms
 - Ultrastructural Study, Hamster, 77-6267

Urea, Hydroxy-

- Quinoline, 4-Nitro-, 1-Oxide
 - Cell Transformation, Neoplastic, 77-6288
 - DNA Repair, 77-6288

Urea, Methyl Nitroso-

- Brain Neoplasms
 - Histological Study, 77-6002
- Bronchial Neoplasms
 - Azathioprine, 77-6215
 - Precancerous Conditions, 77-6215
 - Prednisolone, Methyl-, 77-6215
- Carbamic Acid, Diethyldithio-
 - DNA, Liver, 77-6254
- Cysteine
 - Carcinogenic Activity, Nitrosamides, 77-6284
- DNA
 - Purine, 2-Amino-6-methoxy-, 77-6276
- Escherichia coli*
 - DNA, 77-6278
- Guanyl Cyclase
 - Colon, Liver, Rat, 77-6273
- Kidney Neoplasms
 - Carcinogenic Activity, 77-6069
- Liver Neoplasms
 - Angiosarcoma, 77-6277
 - Cholangioma, 77-6277
 - Histological Study, Guinea Pig, 77-6277
- Lymphosarcoma
 - Histological Study, Guinea Pig, 77-6277
- Mammary Neoplasms, Experimental
 - Dietary Fats, 77-6234
- Metabolism
 - Carcinogenic Activity, 77-6069
 - Mutagenic Activity, 77-6069
- Nervous System Neoplasms
 - Carcinogenic Activity, 77-6069
- Purine, 2-Amino-6-methoxy-
 - Brain, Rat, 77-6276
- Respiratory Tract Neoplasms
 - Ultrastructural Study, Hamster, 77-6267

Urea, 1,1,3-Trimethyl-3-nitroso-

- Brain Neoplasms
 - Histological Study, 77-6002

Uridine, 5-Bromo-2'-deoxy-

- Fibrosarcoma
 - Cholanthrene, 3-Methyl-, 77-6153
- Melanoma
 - Virus Replication, 77-6153
- Neoplasms, Experimental
 - Neoplasm Transplantation, 77-6153
 - Virus Replication, 77-6153
- Virus, Epstein-Barr
 - Cell Transformation, Neoplastic, 77-6407

Uridine, 5-Bromo-2'-deoxy- (cont'd)

- Virus, Friend Murine Leukemia
 - Cell Transformation, Neoplastic, 77-6153
- Virus, Murine Leukemia
 - RNA Replication, 77-6367
- Virus, Murine Sarcoma
 - RNA Replication, 77-6367

Uridine, 2'-Deoxy-5-iodo-

- Antigens, Viral
 - Organ Culture, 77-6353
- Fibrosarcoma
 - Cholanthrene, 3-Methyl-, 77-6153
- Melanoma
 - Virus Replication, 77-6153
- Neoplasms, Experimental
 - Neoplasm Transplantation, 77-6153
 - Virus Replication, 77-6153
- Virus, Friend Murine Leukemia
 - Cell Transformation, Neoplastic, 77-6153
- Virus, Kirsten Murine Sarcoma
 - Reverse Transcriptase, 77-6370

Urinary Tract Infections

- Bladder Neoplasms
 - Nitrosamines, 77-6266

Urine

- 2-Biphenylamine
 - Mutagenic Activity, 77-6138
- Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 - Mutagenic Activity, 77-6138
- 2-Imidazolidinethione
 - Metabolites, 77-6282
- Virus, Papova
 - Case Report, 77-6384
 - Pregnancy, 77-6385
- Virus, Polyoma
 - Case Report, 77-6384
 - Pregnancy, 77-6385
 - Ultrastructural Study, 77-6384

Urogenital Neoplasms

- Neoplasm Metastasis
 - Ultrastructural Study, Crab, 77-6568
- Neoplasms, Multiple Primary
 - Case Report, 77-6551
 - Genetics, 77-6551
- Water Pollution
 - Epidemiology, Crab, 77-6568

Uterine Neoplasms

- Carcinoma
 - Estradiol, 77-6030
 - Estrogens, 77-6032, 77-6033
- Estrogens
 - Epidemiology, 77-6031
 - Review, 77-6034
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Review, 77-6034

Vagina

- Virus, Polyoma
 - Case Report, 77-6384
 - Ultrastructural Study, 77-6384

Vaginal Neoplasms

- Adenocarcinoma
 - 4,4'-Stilbenediol, α,α' -Diethyl-, 77-6113
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Transplacental Carcinogenesis, 77-6113

Valeric Acid, 2,2-Diphenyl-, 2-(Diethylamino)ethyl Ester HCl
Dimethylamine, *N*-Nitroso-
1-Propanone, 2-Methyl-1,2-di-3-pyridyl-, Tartrate
77-6258

Vincaloeukoblastine, Sulfate
Lymphoid Tissue
Rosette Formation, Chick, 77-6472

Viral Interference
Virus, Marek's Disease Herpes
Immune Response, 77-6329

Viral Proteins

DNA

Binding, 77-6366, 77-6371, 77-6394

Genetics

Models, Theoretical, 77-6108

Interferon

Virus, SV40, 77-6422

RNA

Binding, 77-6366

Virus, Adeno 5

DNA, 77-6394

Virus, Avian Myeloblastosis

Antigens, Viral, 77-6324

Isolation and Characterization, 77-6315, 77-6319
77-6325

RNA, Viral, 77-6319

Virus, Avian Sarcoma

Cells, Cultured, 77-6308

Virus, C-Type RNA Tumor

Chromosome Mapping, 77-6360

Isolation and Characterization, 77-6360

Mouse, 77-6351

Virus, Feline Leukemia

Isolation and Characterization, 77-6366

Virus, Friend Murine Leukemia

Antigen-Antibody Reactions, 77-6484

B-Lymphocytes, 77-6484

Virus, Moloney Murine Leukemia

Interferon, 77-6363

Isolation and Characterization, 77-6362, 77-6363

Virus, Moloney Murine Sarcoma

Isolation and Characterization, 77-6366

Virus, Murine Mammary Tumor

Isolation and Characterization, 77-6371, 77-6373
77-6374

Virus, Papova

Isolation and Characterization, 77-6382

Virus, Polyoma

Acetic Acid, (Ethylenebis(oxyethylenenitrilo))tetra-
77-6381

2,3-Butanediol, 1,4-Dimercapto-, 77-6381

Calcium, 77-6381

Ultrastructural Study, Dissociation, 77-6381

Virus, Rauscher Murine Leukemia

Isolation and Characterization, 77-6357, 77-6358
77-6371

Virus, Rous Sarcoma

Isolation and Characterization, 77-6314, 77-6315

RNA, Viral, 77-6314

Virus, SV40

Isolation and Characterization, 77-6382

RNA, Messenger, 77-6417

Virus, Woolly Monkey C-Type

Isolation and Characterization, 77-6371

Viral Vaccines

Lymphoma

Transplantation Immunology, 77-6458

Virus, Avian Leukosis

B-Lymphocytes, 77-6467

Virus, Marek's Disease Herpes

Antigens, Neoplasm, 77-6483

Immune Response, 77-6329

Immunity, Cellular, 77-6483

Virus Replication, 77-6329

Virus, Adeno

Antigenic Determinants

Mouse FL Strain, 77-6335

DNA, Viral

Isolation and Characterization, 77-6335

Mouse FL Strain, 77-6335

Virus Replication

Mouse FL Strain, 77-6335

Virus, Adeno 2

Cells, Cultured

Receptors, KB-Cell, 77-6389

DNA, Viral

Cell Transformation, Neoplastic, 77-6393

Isolation and Characterization, 77-6390

HeLa Cells

Cell-Cycle Kinetics, 77-6391

Virus Replication, 77-6391

Peptides

Cell-Cycle Kinetics, 77-6391

Subcellular Fractions, HeLa Cells, 77-6391

Virus Replication, 77-6391

Receptors, KB-Cell

Isolation and Characterization, 77-6389

RNA, Messenger

DNA, Viral, 77-6392

Virus, Adeno 3

Age Factors

Antibody Formation, 77-6334

Cell Transformation, Neoplastic, 77-6334

Transplantation Immunology, 77-6334

Antilymphocyte Serum

Immune Response, 77-6334

T-Lymphocytes, 77-6334

Histocompatibility Antigens

Immune Response, 77-6334

Mycobacterium bovis

Immune Response, 77-6334

Virus, Adeno 5

Viral Proteins

DNA, 77-6394

Virus, Adeno 12

DNA, Viral

Cell Transformation, Neoplastic, 77-6395, 77-6396

Virus, Adeno-Associated

Virus Replication

Antigens, Viral, 77-6396

Virus, Adeno 7 - SV40 Hybrid

Antigen-Antibody Reactions

Immunity, Cellular, 77-6439

Complement

Antigen-Antibody Reactions, 77-6439

Neoplasms, Experimental

Antigen-Antibody Reactions, 77-6439

- Virus, Adeno 7 - SV40 Hybrid (cont'd)**
 - Immunity, Cellular, 77-6439
- Virus, Avian Leukosis**
 - Antibody Formation
 - Histocompatibility Antigens, 77-6467
 - Antigenic Determinants
 - Cell Transformation, Neoplastic, 77-6481
 - Immunity, Cellular, 77-6481
 - Virus Replication, 77-6481
 - B-Lymphocytes
 - Antibody Formation, 77-6467
 - Cyclophosphamide, 77-6467
 - Histocompatibility Antigens, 77-6467
 - Immune Response, 77-6467
 - Viral Vaccines, 77-6467
 - RNA, Viral
 - Cell Transformation, Neoplastic, 77-6330
- Virus, Avian Myeloblastosis**
 - Antigens, Viral
 - Isolation and Characterization, 77-6325
 - DNA, Viral
 - DNA-RNA Hybridization, 77-6318
 - Virus Replication, 77-6318
 - Reverse Transcriptase
 - Antigens, Viral, 77-6324
 - DNA Replication, 77-6321
 - Enzymatic Activity, 77-6323
 - Isolation and Characterization, 77-6321
 - RNA, Viral
 - Base Sequence, 77-6322
 - Virus Replication, 77-6322
 - Reverse Transcriptase, 77-6320
 - Viral Proteins
 - Antigens, Viral, 77-6324
 - Isolation and Characterization, 77-6315, 77-6319, 77-6325
 - RNA, Viral, 77-6319
- Virus, Avian RNA Tumor**
 - RNA, Viral
 - Isolation and Characterization, 77-6330
- Virus, Avian Sarcoma**
 - Antigenic Determinants
 - Cell Transformation, Neoplastic, 77-6481
 - Immunity, Cellular, 77-6481
 - Virus Replication, 77-6481
 - Antigens, Viral
 - Isolation and Characterization, 77-6312
 - Cell Transformation, Neoplastic
 - Adenosine Cyclic 3',5' Monophosphate, 77-6317
 - Adenyl Cyclase, 77-6317
 - Cholanthrene, 3-Methyl-
 - Immunity, Cellular, 77-6481
 - RNA, Viral
 - Cell Transformation, Neoplastic, 77-6330
 - Cells, Cultured, 77-6311
 - Isolation and Characterization, 77-6311
 - Viral Proteins
 - Cells, Cultured, 77-6308
- Virus, B77**
 - DNA, Viral
 - Binding Sites, 77-6309
 - DNA-RNA Hybridization, 77-6309
- Virus, B-Type RNA Tumor**
 - Guinea Pig
- Virus, B-Type RNA Tumor (cont'd)**
 - Isolation and Characterization, 77-6337
- Virus, Bovine Leukemia**
 - Antigens, Viral
 - Lymphocytes, 77-6087
 - Horizontal Transmission
 - Immune Response, Cattle, 77-6559
 - B-Lymphocytes
 - Syncytia Induction, 77-6332
 - Virus Replication, 77-6332
 - Vertical Transmission
 - Immune Response, Cattle, 77-6559
- Virus, C-Type RNA Tumor**
 - Antigen-Antibody Reactions
 - Immunosuppression, 77-6495
 - Cells, Cultured
 - Antigens, Viral, 77-6349
 - Genetics
 - Cells, Cultured, 77-6343
 - Models, Theoretical, 77-6108
 - Immune Serums
 - Antigen-Antibody Reactions, 77-6495
 - Leukemia
 - Epidemiology, Review, 77-6104
 - Lipopolysaccharides
 - Immune Serums, 77-6495
 - Viral Proteins
 - Chromosome Mapping, 77-6360
 - Isolation and Characterization, 77-6360
 - Mouse, 77-6351
 - Virus Replication
 - Cells, Cultured, 77-6349
- Virus Cultivation**
 - Virus, Herpes
 - Guinea Pig, 77-6338
- Virus, DNA Tumor**
 - Reverse Transcriptase
 - Cell Transformation, Neoplastic, Review, 77-6085
- Virus, Epstein-Barr**
 - Antibodies, Viral
 - Burkitt's Lymphoma, 77-6438
 - Antigens, Viral
 - Baboon, 77-6413
 - Binding, Iodinated Antibodies, 77-6409
 - Burkitt's Lymphoma, 77-6438
 - Chimpanzee, 77-6413
 - Isolation and Characterization, 77-6410, 77-6411
 - Quantitation Method, 77-6409
 - Burkitt's Lymphoma
 - Antigens, Viral, 77-6409, 77-6412
 - Case Report, 77-6557
 - B-Lymphocytes, 77-6565
 - Cell Transformation, Neoplastic
 - Clone Cells, 77-6405
 - Uridine, 5-Bromo-2'-deoxy-, 77-6407
 - DNA, Viral
 - Clone Cells, 77-6405
 - Growth Substances
 - Genome-Negative Lymphoblastoid Cell Line, 77-6408
 - Virus Replication, 77-6408
 - Immunologic Deficiency Syndromes
 - Case Report, 77-6557
 - Infectious Mononucleosis
 - Antigens, Viral, 77-6409

- Virus, Epstein-Barr (cont'd)**
 Leukemia, Myelocytic
 Virus-Like Particles, 77-6414
 Leukocytes
 Cell Transformation, Neoplastic, 77-6405
 Lymphocytes
 Cell Transformation, Neoplastic, 77-6407
 Cells, Cultured, 77-6406
 DNA Replication, 77-6407
 B-Lymphocytes
 Baboon, 77-6413
 Nasopharyngeal Neoplasms
 Antibodies, Viral, 77-6404
 Antigen-Antibody Reactions, 77-6403
 Carcinoma, 77-6404, 77-6412
 Epidemiology, 77-6403
 Plasmacytoma
 Case Report, 77-6557
 Virus Replication
 Serum Dependency, 77-6408
- Virus, Feline Leukemia**
 Antibodies, Viral
 Cats, 77-6440
 Antigens, Viral
 Horizontal Transmission, 77-6331
 Leukocytes, 77-6331
 Viral Proteins
 Isolation and Characterization, 77-6366
- Virus, Friend Murine Leukemia**
 Butyric Acid
 Cell Differentiation, 77-6355
 Cells, Cultured
 Isolation and Characterization, 77-6350
 Erythroleukemia
 Antigens, Viral, 77-6356
 Cell Differentiation, 77-6355
 Immune Serums, 77-6356
 Statolon, 77-6356
 Hemoglobins
 Cell Differentiation, 77-6355
 Hypoxanthine
 Cell Differentiation, 77-6355
 B-Lymphocytes
 Viral Proteins, 77-6484
 Methane, Sulfinylbis-
 Cell Differentiation, 77-6355
 Uridine, 5-Bromo-2'-deoxy-
 Cell Transformation, Neoplastic, 77-6153
 Uridine, 2'-Deoxy-5-iodo-
 Cell Transformation, Neoplastic, 77-6153
 Viral Proteins
 Antigen-Antibody Reactions, 77-6484
- Virus, Gross Murine Leukemia**
 Antigens, Viral
 Mouse, 77-6351
 Leukemia, Lymphocytic
 T-Lymphocytes, 77-6560
 Mouse, AKR, 77-6560
 T-Lymphocytes
 Cell Transformation, Neoplastic, 77-6560
- Virus, Guinea Pig Herpes-Like**
 Cells, Cultured
 Ultrastructural Study, 77-6090
 Leukemia
 Ultrastructural Study, 77-6091
- Virus, Guinea Pig Leukemia-Associated**
 Virus-Like Particles
 Ultrastructural Study, 77-6336
- Virus, Guinea Pig RNA Tumor**
 Cells, Cultured
 Ultrastructural Study, 77-6090
 Leukemia
 Ultrastructural Study, 77-6091
- Virus, Harvey Murine Sarcoma**
 RNA Replication
 Stress, Anaerobic, 77-6367
- Virus, Hepatitis**
 Liver Neoplasms
 Carcinoma, 77-6387
- Virus, Hepatitis B**
 Hepatoma, 77-6388
- Virus, Herpes**
 Antigenic Determinants
 Guinea Pig, 77-6338
 Cell Transformation, Neoplastic
 Guinea Pig, 77-6338
 Leukemia, Lymphoblastic
 Isolation and Characterization, Guinea Pig, 77-6338
 Leukemia, Myelocytic
 Chromosome Aberrations, Orangutan, 77-6414
 Virus-Like Particles, 77-6414
 Virus Cultivation
 Guinea Pig, 77-6338
- Virus, Herpes Simplex**
 Agammaglobulinemia
 Killer Cells, 77-6435
 IgG
 Immunity, Cellular, 77-6435
 B-Lymphocytes, 77-6435
 T-Lymphocytes, 77-6435
 Immunity, Cellular
 Immunoglobulins, Fc, 77-6435
 Killer Cells, 77-6435
 Leukocytes
 Killer Cells, 77-6435
 B-Lymphocytes
 Lymphocyte Depletion, 77-6435
 T-Lymphocytes
 Immunity, Cellular, 77-6435
 Lymphocyte Depletion, 77-6435
- Virus, Herpes Simplex 1**
 Antibody Formation
 Effector Cell, 77-6486
 Antigens, Viral
 Cells, Cultured, 77-6397
 Chromosome Aberrations
 Cells, Cultured, 77-6399
 DNA, Viral
 Carcinogenic Potential, Review, 77-6089
 Cells, Cultured, 77-6398
 Nucleic Acid Hybridization, 77-6398
 Gamma Globulins
 Antibody Formation, 77-6486
 IgG
 Antibody Formation, 77-6486
 Immunity, Cellular
 Antigen-Antibody Reactions, 77-6486
 Immunoglobulins, Fc
 Antibody Formation, 77-6486

Virus, Herpes Simplex 2

- Antibodies, Viral
 - Antigen-Antibody Reactions, 77-6401
 - Immunosorbent Assay, 77-6401
- Antigens, Viral
 - Cells, Cultured, 77-6397
- Cell Transformation, Neoplastic
 - Hamster, 77-6088
- Cells, Cultured
 - Ultrastructural Study, 77-6400
- Cervix Neoplasms
 - Carcinoma, 77-6088, 77-6487
 - Epidemiology, 77-6487
 - Epidemiology, Review, 77-6089
- Chromosome Aberrations
 - Cells, Cultured, 77-6399
- DNA, Viral
 - Carcinogenic Potential, Review, 77-6089
- Fibrosarcoma
 - Hamster, 77-6088
- Thymidine Kinase
 - Cells, Cultured, 77-6402
 - Chromosomes, 77-6402
 - Enzymatic Activity, 77-6402

Virus, Kirsten Murine Sarcoma

- Cell Transformation, Neoplastic
 - Cell Membrane, 77-6369
- Guinea Pig
 - Isolation and Characterization, 77-6337
- Reverse Transcriptase
 - Dexamethasone, 77-6370
 - Interferon, 77-6370
 - Uridine, 2'-Deoxy-5-iodo-, 77-6370
- RNA Replication
 - Stress, Anaerobic, 77-6367

Virus-Like Particles

- Cells, Cultured
 - Isolation and Characterization, 77-6339
- Esophageal Neoplasms
 - Carcinoma, Epidermoid, 77-6508
- Leukemia, Myelocytic
 - Virus, Epstein-Barr, 77-6414
 - Virus, Herpes, 77-6414
- Ovarian Neoplasms
 - Radiation, Ionizing, 77-6342
 - Ultrastructural Study, 77-6342
- Plasmacytoma
 - RNA, Viral, 77-6348
- Reverse Transcriptase
 - Cells, Cultured, 77-6339
- RNA Polymerase
 - Enzymatic Activity, 77-6347
- Virus, Guinea Pig Leukemia-associated
 - Ultrastructural Study, 77-6336

Virus, Lucke Herpes

- Antigens, Viral
 - Ultrastructural Study, Ascites Cells, 77-6567
- Kidney Neoplasms
 - Adenocarcinoma, 77-6567
 - Antigen-Antibody Reactions, 77-6567
 - Cell Aggregation, 77-6567
 - Ultrastructural Study, Ascites Cells, 77-6567

Virus, Marek's Disease Herpes

- Antigens, Neoplasm
 - Viral Vaccines, 77-6483

Virus, Marek's Disease Herpes (cont'd)

- Genetics
 - Chicken, 77-6328, 77-6482
- Histocompatibility Antigens
 - Chicken, 77-6482
- Neoplasm Transplantation
 - Chicken, 77-6328
- Viral Interference
 - Immune Response, 77-6329
- Viral Vaccines
 - Antigens, Neoplasm, 77-6483
 - Immune Response, 77-6329
 - Immunity, Cellular, 77-6483
 - Virus Replication, 77-6329
- Virus, Turkey Herpes
 - Antigens, Neoplasm, 77-6483
 - Cell Transformation, Neoplastic, 77-6483
 - Immunity, Cellular, 77-6483

Virus, Moloney Murine Leukemia

- Cells, Cultured
 - Isolation and Characterization, 77-6350
- Interferon
 - Virus Replication, 77-6361
- Reverse Transcriptase
 - Enzymatic Activity, 77-6323
- Viral Proteins
 - Interferon, 77-6363
 - Isolation and Characterization, 77-6362, 77-6363
- Virus, Moloney Murine Sarcoma
 - DNA-RNA Hybridization, 77-6364
 - RNA, Viral, 77-6364
- Virus Replication
 - Ultrastructural Study, 77-6361

Virus, Moloney Murine Sarcoma

- Cell Transformation, Neoplastic
 - Fluorescamine Labeling, 77-6340
- Histocompatibility Antigens
 - Migration Inhibitory Factor, 77-6486
- T-Lymphocytes
 - Migration Inhibitory Factor, 77-6486
- Macrophages
 - Histocompatibility Antigens, 77-6486
 - T-Lymphocytes, 77-6486
- Sarcoma, Osteogenic
 - Alkaline Phosphatase, 77-6365
 - Histological Study, 77-6365
 - Hypercalcemia, 77-6365
 - Proline, 4-Hydroxy, 77-6365
 - Ultrastructural Study, 77-6365
- Viral Proteins
 - Isolation and Characterization, 77-6366
- Virus, Moloney Murine Leukemia
 - DNA-RNA Hybridization, 77-6364
 - RNA, Viral, 77-6364

Virus, Murine Leukemia

- Antigens, Viral
 - Organ Culture, 77-6353
 - Precancerous Conditions, 77-6352
- Cells, Cultured
 - Geldanamycin, 77-6197
 - Isolation and Characterization, 77-6350
 - Leukemia, 77-6354
- Cycloheximide

- Virus, Murine Leukemia (cont'd)**
 RNA Replication, 77-6367
 Leukemia
 Immunity, Cellular, 77-6434
 Lymphoma
 Transplantation Immunology, 77-6458
 RNA Replication
 Stress, Anaerobic, 77-6367
 RNA, Viral
 Isolation and Characterization, 77-6344
 Thymus Gland
 Antigens, Viral, 77-6352
 Precancerous Conditions, 77-6352
 Uridine, 5-Bromo-2'-deoxy-
 RNA Replication, 77-6367
 Virus Replication
 Age Factors, AKR Mouse, 77-6352
- Virus, Murine Mammary Tumor**
 Cell Transformation, Neoplastic
 Genotype, 77-6372
 Cells, Cultured
 Isolation and Characterization, 77-6374
 Ultrastructural Study, 77-6374
 DNA, Viral
 Isolation and Characterization, 77-6376
 Ergocalciferol
 Cell Transformation, Neoplastic, 77-6242
 Dose-Response Study, 77-6242
 Interferon
 Antigens, Viral, 77-6375
 Cells, Cultured, 77-6375
 Reverse Transcriptase, 77-6375
 Mammary Neoplasms, Experimental
 Adenocarcinoma, 77-6372
 Genotype, 77-6372
 Histological Study, 77-6372
 Precancerous Conditions, 77-6111
 Pregnancy, 77-6372
 Pregnancy
 Cell Transformation, Neoplastic, 77-6372
 Reverse Transcriptase
 Isolation and Characterization, 77-6373
 RNA, Viral
 Isolation and Characterization, 77-6374
 Viral Proteins
 Isolation and Characterization, 77-6371, 77-6373
 77-6374
- Virus, Murine Sarcoma**
 Adenosine Cyclic 3',5' Monophosphate
 Cell Transformation, Neoplastic, 77-6368
 Agglutination
 Cell Transformation, Neoplastic, 77-6368
 Cell Transformation, Neoplastic
 Temperature-Sensitive Mutants, 77-6368
 Concanavalin A
 Cell Transformation, Neoplastic, 77-6368
 Cycloheximide
 RNA Replication, 77-6367
 Hexoses
 Cell Transformation, Neoplastic, 77-6368
 Lipids
 Cell Transformation, Neoplastic, 77-6368
 Uridine, 5-Bromo-2'-deoxy-
 RNA Replication, 77-6367
- Virus, Papilloma**
 Bracken Fern
- Virus, Papilloma (cont'd)**
 Epidemiology, Cattle, 77-6178
 Digestive System Neoplasms
 Epidemiology, Cattle, 77-6178
 DNA, Viral
 Isolation and Characterization, 77-6386
 Reassociation Kinetics, 77-6386
 Ultrastructural Study, 77-6386
 Warts
 DNA, Viral, 77-6386
- Virus, Papova**
 Antibodies, Viral
 Bladder Neoplasms, 77-6383
 Neoplasms, 77-6383
 Urine
 Case Report, 77-6384
 Pregnancy, 77-6385
 Viral Proteins
 Isolation and Characterization, 77-6382
- Virus, Polyoma**
 Acetic Acid, (Ethylenebis(oxyethylenitrilo))tetra-
 Viral Proteins, 77-6381
 2,3-Butanediol, 1,4-Dimercapto-
 Viral Proteins, 77-6381
 Calcium
 Viral Proteins, 77-6381
 DNA, Viral
 DNA-RNA Hybridization, 77-6380
 Mouse, 77-6378
 RNA Replication, 77-6380
 Ultrastructural Study, 77-6416
 RNA Replication
 Temperature Sensitive Mutants, 77-6377
 RNA, Viral
 DNA-RNA Hybridization, 77-6379
 Temperature Sensitive Mutants, 77-6377
 Urine
 Case Report, 77-6384
 Pregnancy, 77-6385
 Ultrastructural Study, 77-6384
 Vagina
 Case Report, 77-6384
 Ultrastructural Study, 77-6384
 Viral Proteins
 Ultrastructural Study, Dissociation, 77-6381
- Virus, Polyoma BK**
 Antibodies, Viral
 Pregnancy, 77-6385
- Virus, Polyoma JC**
 Antibodies, Viral
 Pregnancy, 77-6385
- Virus, Pox**
 Methotrexate
 Virus Replication, 77-6294
- Virus, Radiation Leukemia**
 Histocompatibility Antigens
 Immune Response, 77-6346
 Lymphoma
 Isolation and Characterization, 77-6345
 Mouse, 77-6345
- Virus, Rauscher Murine Leukemia**
 Carbon
 Cell Transformation, Neoplastic, 77-6466
 Carrageen

Virus, Rauscher Murine Leukemia (cont'd)
 Cell Transformation, Neoplastic, 77-6466
 Macrophages
 Immune Response, 77-6466
 Leukocyte Sequestration, 77-6466
 Phagocytosis, 77-6466
 Streptovaricins
 Reverse Transcriptase, 77-6359
 Viral Proteins
 Isolation and Characterization, 77-6357, 77-6358
 77-6371

Virus Replication

DNA Polymerase
 Isolation and Characterization, 77-6424
 Interferon
 Virus, SV40, 77-6422
 Melanoma
 Uridine, 5-Bromo-2'-deoxy-, 77-6153
 Uridine, 2'-Deoxy-5-iodo-, 77-6153
 Neoplasms, Experimental
 Uridine, 5-Bromo-2'-deoxy-, 77-6153
 Uridine, 2'-Deoxy-5-iodo-, 77-6153
 Virus, Adeno
 Mouse FL Strain, 77-6335
 Virus, Adeno 2
 HeLa Cells, 77-6391
 Peptides, 77-6391
 Virus, Adeno-Associated
 Antigens, Viral, 77-6396
 Virus, Avian Leukosis
 Antigenic Determinants, 77-6481
 Virus, Avian Myeloblastosis
 DNA, Viral, 77-6318
 RNA, Viral, 77-6322
 Virus, Avian Sarcoma
 Antigenic Determinants, 77-6481
 Virus, Bovine Leukemia
 B-Lymphocytes, 77-6332
 Virus, C-Type RNA Tumor
 Cells, Cultured, 77-6349
 Virus, Epstein-Barr
 Growth Substances, 77-6408
 Serum Dependency, 77-6408
 Virus, Marek's Disease Herpes
 Viral Vaccines, 77-6329
 Virus, Moloney Murine Leukemia
 Interferon, 77-6361
 Ultrastructural Study, 77-6361
 Virus, Murine Leukemia
 Age Factors, AKR Mouse, 77-6352
 Virus, Pox
 Methotrexate, 77-6294
 Virus, RNA Tumor
 Cells, Cultured, 77-6326
 Mouse, 77-6341
 Virus, Sindbis
 Cells, Cultured, 77-6326
 Virus, SV40
 DNA Polymerase, 77-6424
 Mitomycin C, 77-6415
 RNA, 77-6432
 Virus, Visna
 RNA, Viral, 77-6333

Virus, RNA Tumor

Breast Neoplasms
 Epidemiology, 77-6116

Virus, RNA Tumor (cont'd)

Cells, Cultured
 Virus Replication, 77-6326
 Leukemia
 Mouse, 77-6341
 Mammary Neoplasms, Experimental
 Mouse, 77-6341
 Neoplasm Transplantation
 Mouse, 77-6341
 Reverse Transcriptase
 Cell Transformation, Neoplastic, Review, 77-6085
 Ultrastructural Study
 Mouse, 77-6341
 Virus Replication
 Mouse, 77-6341

Virus, Rous-Associated

RNA, Viral
 Cells, Cultured, 77-6316
 Virus, Rous Sarcoma
 Cells, Cultured, 77-6308

Virus, Rous Sarcoma

Cell Transformation, Neoplastic
 Isolation and Characterization, 77-6307
 Phosphatidyl Inositol, 77-6310
 RNA, Messenger, 77-6313
 DNA, Viral
 Binding Sites, 77-6309
 DNA-RNA Hybridization, 77-6309
 Estr-4-en-3-one, 7 α ,17-Dimethyl-17 β -Hydroxy
 Antibody Formation, 77-6453
 Bursa of Fabricius, 77-6453
 Cell Transformation, Neoplastic, 77-6453
 Hematopoietic Stem Cells, 77-6453
 Immunity, Cellular, 77-6453
 Glucosamine
 Peptides, 77-6307
 Glucose, 2-Deoxy-
 Peptides, 77-6307
 Peptides
 Cell Membrane, 77-6307
 Cell Transformation, Neoplastic, 77-6307
 Phosphatidyl Inositol
 Metabolism, 77-6310
 Reverse Transcriptase
 Enzymatic Activity, 77-6323
 RNA, Viral
 Cells, Cultured, 77-6316
 Viral Proteins, 77-6314
 Viral Proteins
 Isolation and Characterization, 77-6314, 77-6315
 Virus, Rous-Associated
 Cells, Cultured, 77-6308

Virus, Shope Papilloma

Papilloma
 Rabbit, 77-6496

Virus, Sindbis

Cells, Cultured
 Virus Replication, 77-6326

Virus, SV40

Antigens, Neoplasm
 Immune Response, 77-6441
 Antigens, Viral
 Antigen-Antibody Reactions, 77-6426
 Antigenic Determinants, 77-6426
 Carcinoembryonic Antigen, 77-6426

Virus, SV40 (cont'd)

- Cell Transformation, Neoplastic, 77-6426
- DNA Replication, 77-6419
- Temperature Sensitive Mutants, 77-6428, 77-6429
- Cell Membrane
 - Antigens, Viral, 77-6427
 - Cell Transformation, Neoplastic, 77-6595
 - Histocompatibility Antigens, 77-6427
- Cell Nucleus
 - Histocompatibility Antigens, 77-6427
- Cell Transformation, Neoplastic
 - Cell Membrane, 77-6430
 - Contact Inhibition, 77-6588
 - Fluorescamine Labeling, 77-6340
 - Migration Inhibitory Factor, 77-6464
- Chromosome Aberrations
 - Cell Transformation, Neoplastic, 77-6553
- DNA
 - Base Sequence, 77-6417
- DNA Polymerase
 - Cells, Cultured, 77-6424
 - Virus Replication, 77-6424
- DNA Replication
 - Temperature Sensitive Mutants, 77-6420
- DNA, Viral
 - Genetics, 77-6433
 - Isolation and Characterization, 77-6419
 - RNA Polymerase, 77-6425
 - Ultrastructural Study, 77-6416, 77-6418
- Histocompatibility Antigens
 - Cell Transformation, Neoplastic, 77-6427
 - Transplantation Immunology, 77-6427
- Histones
 - Metabolism, 77-6423
- Hypoxanthine Phosphoribosyltransferase
 - Cell Transformation, Neoplastic, 77-6595
- Interferon
 - Viral Proteins, 77-6422
 - Virus Replication, 77-6422
- Myosin
 - Cell Transformation, Neoplastic, 77-6421
 - Phosphotransferases, 77-6421
 - Temperature Sensitive Mutants, 77-6421
- Neoplasms, Experimental
 - T-Lymphocytes, 77-6448
 - Transplantation Immunology, 77-6448
- Neuroglia
 - Myosin, 77-6421
- Nucleotides
 - Cell Transformation, Neoplastic, 77-6595
- Proteins
 - Degradation, Intracellular, 77-6588
- RNA
 - Uracil Nucleotides, 77-6432
 - Uridine Incorporation, 77-6432
 - Virus Replication, 77-6432
- RNA, Messenger
 - Base Sequence, 77-6417
 - Viral Proteins, 77-6417
- RNA, Viral
 - Isolation and Characterization, 77-6425
 - RNA Polymerase, 77-6425
 - Temperature Sensitive Mutants, 77-6420
- Temperature Sensitive Mutants
 - Isolation and Characterization, 77-6428
- Teratoid Tumor
 - Cell Differentiation, 77-6431

Virus, SV40 (cont'd)

- Cell Transformation, Neoplastic, 77-6431
- Creatine Kinase, 77-6431
- Plasminogen, 77-6431
- Viral Proteins
 - Isolation and Characterization, 77-6382
- Virus Replication
 - Mitomycin C, 77-6415

Virus, Turkey Herpes

- Virus, Marek's Disease Herpes
 - Antigens, Neoplasm, 77-6483
 - Cell Transformation, Neoplastic, 77-6483
 - Immunity, Cellular, 77-6483

Virus, Visna

- RNA, Viral
 - Isolation and Characterization, 77-6333
- Virus Replication, 77-6333

Virus, Woolly Monkey C-Type

- Viral Proteins
 - Isolation and Characterization, 77-6371

Vitamin C

- see Ascorbic Acid

Vitamin D2

- see Ergocalciferol

Warts

- Virus, Papilloma
 - DNA, Viral, 77-6386

Water Pollutants

- Chloroform
 - Toxicology, 77-6155
- Ether, Bis(2-chloro-1-methylethyl)-
 - Metabolism, Monkey, Rat, 77-6154
- Lead
 - Isolation and Characterization, 77-6585
- Petroleum
 - Mutagenic Activity, 77-6296

Water Pollution

- Asbestos
 - Legal Aspects, Review, 77-6021
- Benzo(a)pyrene
 - Review, 77-6025
- Cadmium
 - Review, 77-6025
- Carbon Tetrachloride
 - Review, 77-6025
- Carcinogen, Environmental
 - Fish, 77-6586
 - Legal Aspects, Review, 77-6021
- Chlorine
 - Carcinogenic Potential, Review, 77-6026
- Chloroform
 - Carcinogenic Potential, 77-6027
 - Epidemiology, 77-6584
- Ethane, Tetrachloro-
 - Review, 77-6025
- Ethane, 1,1,1-Trichloro-2,2-bis(p-chlorophenyl)-
 - Review, 77-6025
- Fertilizers
 - Carcinogenic Potential, Review, 77-6022
- Lead
 - Review, 77-6025

Water Pollution (cont'd)

Mercury

Isolation and Characterization, 77-6585

Review, 77-6025

Mutagens

Carcinogenic Potential, Review, 77-6026

Neoplasms, Connective Tissue

Epidemiology, Crab, 77-6568

Ozone

Carcinogenic Potential, Review, 77-6026

Pesticides

Carcinogenic Potential, Review, 77-6022

Plutonium

Review, 77-6025

Polychlorobiphenyl Compounds

Review, 77-6025

Polycyclic Hydrocarbons

Review, 77-6025

Stomach Neoplasms

Nitrous Acid, 77-6068

Urogenital Neoplasms

Epidemiology, Crab, 77-6568

Zinc

Review, 77-6025

Wood

Nose Neoplasms

Epidemiology, 77-6579

Xeroderma Pigmentosum

Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-

Chromosome Aberrations, 77-6287

DNA Repair, 77-6287

Carcinoma, Basal Cell

Radiation-Protective Agents, 77-6521

Chromosome Aberrations

Cells, Cultured, 77-6287

Daunomycin

Chromosome Aberrations, 77-6287

Guanidine, 1-Methyl-3-nitro-1-nitroso-

Chromosome Aberrations, 77-6287

DNA Repair, 77-6287

Quinoline, 4-Nitro-, 1-Oxide

Chromosome Aberrations, 77-6287

DNA Repair, 77-6287

Zinc

Water Pollution

Review, 77-6025

SECTION N. OF 1. IRRAWADDI RIVER
CHARTERED BY THE GOVERNMENT OF BURMA

Chemical Abstracts Service Registry Number Index

50-02-2, 77-6370	55-18-5, 77-6004, 77-6063, 77-6065 77-6214, 77-6236, 77-6249 77-6250, 77-6251, 77-6252 77-6253, 77-6267	62-75-9, 77-6009, 77-6063, 77-6064 77-6065, 77-6069, 77-6254 77-6255, 77-6256, 77-6257 77-6258, 77-6259, 77-6267 77-6268, 77-6298
50-06-6, 77-6004, 77-6009, 77-6198 77-6212, 77-6258	55-80-1, 77-6136, 77-6494	64-17-5, 77-6181, 77-6182
50-07-7, 77-6293, 77-6415, 77-6455	56-23-5, 77-6025	65-45-2, 77-6204
50-14-6, 77-6242	56-29-1, 77-6180	66-27-3, 77-6005, 77-6254, 77-6257
50-18-0, 77-6452	56-49-5, 77-6099, 77-6153, 77-6194 77-6195, 77-6196, 77-6197 77-6198, 77-6247, 77-6258 77-6448, 77-6451, 77-6455 77-6459, 77-6481, 77-6490 77-6492, 77-6493, 77-6528 77-6553, 77-6599	66-81-9, 77-6291, 77-6367, 77-6588
50-27-1, 77-6118	56-53-1, 77-6028, 77-6029, 77-6034 77-6113, 77-6227, 77-6228 77-6229	67-21-0, 77-6164
50-28-2, 77-6030, 77-6118, 77-6203 77-6229, 77-6230, 77-6233	56-55-3, 77-6212	67-42-5, 77-6381
50-29-3, 77-6025	56-57-5, 77-6273, 77-6287, 77-6288	67-63-0, 77-6054
50-32-8, 77-6010, 77-6013, 77-6016 77-6018, 77-6025, 77-6042 77-6061, 77-6180, 77-6182 77-6198, 77-6199, 77-6201 77-6204, 77-6205, 77-6209 77-6210, 77-6211, 77-6212 77-6213, 77-6214, 77-6215 77-6216, 77-6222, 77-6298 77-6340, 77-6445, 77-6492 77-6528, 77-6582	56-69-9, 77-6060	67-66-3, 77-6027, 77-6155, 77-6584
50-44-2, 77-6293, 77-6295	56-73-5, 77-6251	67-68-5, 77-6355
50-67-9, 77-6247	57-14-7, 77-6170, 77-6171, 77-6184	68-26-8, 77-6273
50-81-7, 77-6064, 77-6147	57-41-0, 77-6060	68-94-0, 77-6355
51-21-8, 77-6293	57-57-8, 77-6240	70-25-7, 77-6005, 77-6067, 77-6271 77-6272, 77-6273, 77-6287
51-31-0, 77-6070	57-63-6, 77-6035	71-43-2, 77-6104, 77-6125, 77-6144 77-6145
51-35-4, 77-6365	57-83-0, 77-6037, 77-6038, 77-6203 77-6235, 77-6236	72-33-3, 77-6035
51-41-2, 77-6247	57-85-2, 77-6245	72-57-1, 77-6444
51-48-9, 77-6226	57-88-5, 77-6037, 77-6122, 77-6233 77-6592	72-63-9, 77-6244
51-52-5, 77-6226	57-97-6, 77-6198, 77-6203, 77-6444 77-6447, 77-6457, 77-6492 77-6529	73-22-3, 77-6139, 77-6140
51-61-6, 77-6247	58-08-2, 77-6290, 77-6291	75-01-4, 77-6013, 77-6039, 77-6113 77-6157
51-75-2, 77-6001	58-22-0, 77-6112, 77-6243, 77-6246 77-6452, 77-6513	75-09-2, 77-6290
51-79-6, 77-6162, 77-6163, 77-6267	58-32-2, 77-6549	75-35-4, 77-6039
52-90-4, 77-6284	58-89-9, 77-6205	79-01-6, 77-6039
53-03-2, 77-6246	59-14-3, 77-6153, 77-6367, 77-6407	81-07-2, 77-6059
53-16-7, 77-6030, 77-6118, 77-6233 77-6528	59-92-7, 77-6060	83-43-2, 77-6215
53-70-3, 77-6013	60-11-7, 77-6456	84-65-1, 77-6179
53-95-2, 77-6254	60-80-0, 77-6180	85-01-8, 77-6200
53-96-3, 77-6018, 77-6135, 77-6136 77-6241	60-92-4, 77-6317, 77-6368, 77-6588	90-41-5, 77-6138
54-12-6, 77-6139, 77-6140	61-80-3, 77-6180	90-43-7, 77-6148, 77-6150
54-16-0, 77-6247	62-55-5, 77-6132, 77-6133	91-59-8, 77-6286
54-36-4, 77-6258	62-68-0, 77-6258	91-64-5, 77-6180
54-42-2, 77-6153, 77-6353, 77-6370		92-52-4, 77-6148, 77-6150
54-80-8, 77-6241		92-67-1, 77-6147, 77-6286
		92-69-3, 77-6148, 77-6150
		92-88-6, 77-6148
		93-76-5, 77-6051, 77-6161
		94-59-7, 77-6146, 77-6150
		94-75-7, 77-6052

96-09-3, 77-6158
 96-12-8, 77-6044
 96-45-7, 77-6282, 77-6283
 97-53-0, 77-6146
 97-56-3, 77-6013
 97-77-8, 77-6212
 99-96-7, 77-6062
 103-90-2, 77-6018
 106-14-9, 77-6165
 106-51-4, 77-6049
 106-93-4, 77-6041
 107-02-8, 77-6214
 107-30-2, 77-6071
 107-92-6, 77-6355
 108-30-5, 77-6057
 108-46-3, 77-6042
 110-97-4, 77-6263, 77-6264, 77-6265
 115-02-6, 77-6166, 77-6167
 118-00-3, 77-6275
 120-12-7, 77-6200, 77-6210
 120-80-9, 77-6042
 123-31-9, 77-6042
 123-33-1, 77-6184
 126-99-8, 77-6159
 127-07-1, 77-6288
 127-47-9, 77-6212, 77-6230
 128-37-0, 77-6162
 129-00-0, 77-6200
 134-32-7, 77-6286
 140-57-8, 77-6160
 140-67-0, 77-6146
 140-79-4, 77-6269
 141-05-9, 77-6204
 141-23-1, 77-6165
 143-67-9, 77-6472
 147-84-2, 77-6254
 148-82-3, 77-6295
 154-17-6, 77-6307
 154-93-8, 77-6281
 218-01-9, 77-6201, 77-6202
 262-12-4, 77-6040
 302-01-2, 77-6273
 334-88-3, 77-6275
 366-70-1, 77-6295

398-32-3, 77-6134
 434-07-1, 77-6513
 434-13-9, 77-6297
 446-86-6, 77-6215
 471-29-4, 77-6274
 519-23-3, 77-6206
 540-61-4, 77-6254
 540-73-8, 77-6121, 77-6169, 77-6298
 77-6566
 542-88-1, 77-6154
 548-26-5, 77-6055
 553-24-2, 77-6306
 566-28-9, 77-6592
 580-51-8, 77-6148
 592-62-1, 77-6143, 77-6254
 604-59-1, 77-6180, 77-6204, 77-6212
 607-30-7, 77-6286
 613-13-8, 77-6198, 77-6297
 613-47-8, 77-6286
 615-53-2, 77-6284
 635-65-4, 77-6142
 651-48-9, 77-6531
 671-16-9, 77-6295
 684-93-5, 77-6002, 77-6069, 77-6215
 77-6234, 77-6254, 77-6267
 77-6273, 77-6276, 77-6277
 77-6278, 77-6284
 758-17-8, 77-6172
 759-73-9, 77-6002, 77-6069, 77-6267
 77-6279, 77-6280, 77-6491
 764-41-0, 77-6046
 869-01-2, 77-6002
 908-35-0, 77-6258
 926-93-2, 77-6537
 930-55-2, 77-6065
 1116-54-7, 77-6184
 1162-65-8, 77-6058, 77-6174, 77-6254
 77-6298
 1163-19-5, 77-6151
 1299-90-7, 77-6025
 1309-64-4, 77-6151
 1313-59-3, 77-6224
 1327-53-3, 77-6151, 77-6222
 1332-21-4, 77-6021, 77-6073, 77-6074
 77-6113, 77-6465, 77-6577
 77-6578
 1404-00-8, 77-6292

1404-74-6, 77-6359
 1407-15-4, 77-6287, 77-6293
 1596-84-5, 77-6168
 1746-01-6, 77-6040
 2140-46-7, 77-6592
 2179-37-5, 77-6549
 2385-85-5, 77-6050
 2422-79-9, 77-6201
 2439-10-3, 77-6274
 3083-23-6, 77-6204, 77-6213
 3268-87-9, 77-6040
 3416-24-8, 77-6307
 3475-63-6, 77-6002
 3483-12-3, 77-6381
 3697-24-3, 77-6200, 77-6201
 3704-09-4, 77-6453
 3771-19-5, 77-6285
 3817-11-6, 77-6003, 77-6260, 77-6261
 77-6262
 4244-47-7, 77-6240
 4342-03-4, 77-6295
 4759-48-2, 77-6260
 6098-44-8, 77-6005, 77-6254, 77-6287
 77-6303
 6452-71-7, 77-6241
 6493-05-6, 77-6549
 6610-08-8, 77-6286
 6810-26-0, 77-6147
 7439-92-1, 77-6025, 77-6217, 77-6219
 77-6585
 7439-96-5, 77-6217
 7439-97-6, 77-6025, 77-6585
 7440-02-0, 77-6581
 7440-07-5, 77-6025
 7440-14-4, 77-6077, 77-6300
 7440-22-4, 77-6220
 7440-35-9, 77-6075
 7440-38-2, 77-6014, 77-6222, 77-6223
 7440-43-9, 77-6025, 77-6217, 77-6220
 7440-44-0, 77-6466
 7440-48-4, 77-6217
 7440-50-8, 77-6217
 7440-57-5, 77-6220
 7440-65-5, 77-6025
 7440-66-6, 77-6025

7440-70-2, 77-6299, 77-6381	9035-50-1, 77-6018, 77-6206, 77-6258 77-6259	24554-26-5, 77-6003, 77-6138, 77-6139
7631-86-9, 77-6444	10028-15-6, 77-6026	25013-16-5, 77-6273
7631-99-4, 77-6269	10028-16-7, 77-6076	25104-18-1, 77-6600
7632-00-0, 77-6274	10043-66-0, 77-6226	25869-98-1, 77-6299
7665-99-8, 77-6273	10045-97-3, 77-6299	26241-63-4, 77-6135
7697-37-2, 77-6066, 77-6067	10098-97-2, 77-6299	27858-07-7, 77-6015
7726-95-6, 77-6152	10108-64-2, 77-6218	29446-15-9, 77-6040
7778-50-9, 77-6221	10125-76-5, 77-6147	30746-58-8, 77-6040
7782-49-2, 77-6076	11006-77-2, 77-6356	31005-02-4, 77-6180
7782-50-5, 77-6026	11028-71-0, 77-6192, 77-6368	31828-93-0, 77-6197
7782-77-6, 77-6063, 77-6066, 77-6067 77-6068	12001-28-4, 77-6021, 77-6073, 77-6074 77-6113, 77-6465, 77-6577 77-6578	33423-92-6, 77-6040
8002-05-9, 77-6225, 77-6296	12001-29-5, 77-6021, 77-6073, 77-6074 77-6113, 77-6465, 77-6577 77-6578	33857-26-0, 77-6040
8015-95-0, 77-6289, 77-6460, 77-6461 77-6466	12059-95-9, 77-6224	33857-28-2, 77-6040
9000-07-1, 77-6289, 77-6460, 77-6466 77-6471	12172-73-5, 77-6021, 77-6073, 77-6074 77-6113, 77-6465, 77-6577 77-6578	34816-53-0, 77-6040
9001-63-2, 77-6289	13256-13-8, 77-6248	35822-46-9, 77-6040
9001-66-5, 77-6247	13256-32-1, 77-6002	37574-47-3, 77-6061, 77-6207
9001-67-6, 77-6472	13483-18-6, 77-6047	38178-38-0, 77-6040
9001-78-9, 77-6365	14038-43-8, 77-6299	38571-73-2, 77-6045
9001-91-6, 77-6431, 77-6464, 77-6596	14930-96-2, 77-6472	38964-22-6, 77-6040
9002-07-7, 77-6470, 77-6472, 77-6589	16395-80-5, 77-6284	39227-53-7, 77-6040
9002-60-2, 77-6174, 77-6534	16561-29-8, 77-6010	39227-54-8, 77-6040
9002-62-4, 77-6203, 77-6233, 77-6234 77-6235	17068-78-9, 77-6021, 77-6073, 77-6074 77-6113, 77-6465, 77-6577 77-6578	39227-58-2, 77-6040
9002-71-5, 77-6226	18883-66-4, 77-6295	40321-76-4, 77-6040
9004-10-8, 77-6174, 77-6203	20535-83-5, 77-6276	50585-39-2, 77-6040
9005-38-3, 77-6299	20830-81-3, 77-6287, 77-6293	50585-46-1, 77-6040
9005-80-5, 77-6475	21711-65-9, 77-6286	53555-02-5, 77-6040
9006-04-6, 77-6583	22467-31-8, 77-6175	59963-01-8, 77-6208
9008-11-1, 77-6361, 77-6363, 77-6370 77-6375, 77-6422		60784-46-5, 77-6281
9012-42-4, 77-6317		

THE FIDELITY

Wiswesser Line Notation Index

.AG, 77-6220
 .AM, 77-6075
 .AS, 77-6014, 77-6222, 77-6223
 .AS2.O3, 77-6222
 .AU, 77-6220
 .BR, 77-6152
 .C, 77-6466
 .CA, 77-6299, 77-6381
 .CD, 77-6025, 77-6217, 77-6220
 .CD.G2, 77-6218
 .CO, 77-6217
 .CS, 77-6299
 .CU, 77-6217
 .HG, 77-6025, 77-6585
 .I, 77-6226
 .KA2.CR2-05-Q2, 77-6221
 .MN, 77-6217
 .NA..N-O3, 77-6269
 .NA..N-0-Q, 77-6274
 .NI, 77-6581
 .PB, 77-6025, 77-6217, 77-6219, 77-6585
 .PU, 77-6025
 .PU..O2, 77-6224
 .RA, 77-6077, 77-6300
 .SB2.O3, 77-6151
 .SE, 77-6076
 .SI..O2, 77-6444
 .SR, 77-6299
 .TE, 77-6076
 .ZN, 77-6025
 E3E, 77-6041
 FR DR, 77-6134
 GXGGG, 77-6025
 GXGGG YR DG&R DG, 77-6025
 GYGG, 77-6027, 77-6155, 77-6584
 GYGU1, 77-6039
 GYGU1G, 77-6039
 G1G, 77-6290
 G1O1, 77-6071
 G1O1G, 77-6154
 G1U1, 77-6013, 77-6039, 77-6113, 77-6157
 G1YE1E, 77-6044

G2, 77-6026
 G2N1&2G, 77-6001
 G2OSO&OY&1OR DX, 77-6160
 G2U2G, 77-6046
 L B656 HHJ EMV1, 77-6018, 77-6135, 77-6136, 77-6241
 L B656 HHJ ENQV1, 77-6254
 L B666J, 77-6200
 L C666 BV IVJ, 77-6179
 L C666J, 77-6200, 77-6210
 L C666J EZ, 77-6198, 77-6297
 L D6 B666J, 77-6212
 L D6 B666J C, 77-6201
 L D6 B666J C J, 77-6198, 77-6203, 77-6444, 77-6447
 77-6457, 77-6492, 77-6529
 L D6 B6666 2AB TJ, 77-6010, 77-6013, 77-6016, 77-6018
 77-6025, 77-6042, 77-6061, 77-6180, 77-6182
 77-6198, 77-6199, 77-6201, 77-6204, 77-6205
 77-6209, 77-6210, 77-6211, 77-6212, 77-6213
 77-6214, 77-6215, 77-6216, 77-6222, 77-6298
 77-6340, 77-6445, 77-6492, 77-6528, 77-6582
 L E5 B666 FVTTT&J E OQ, 77-6030, 77-6118, 77-6233
 77-6528
 L E5 B666 LUTJ A E FY&3Y QQ -B&AEFO, 77-6037
 77-6122, 77-6233, 77-6592
 L E5 B666 OV MU PUTJ A1 CQ E1 FV1Q FQ L1 -
 B&ACEF
 77-6215
 L E5 B666 OV MUTJ A E FQ -B&AEF, 77-6112, 77-6243
 77-6246, 77-6452, 77-6513
 L E5 B666 OV MUTJ A1 E1 FV1 -B&AEF, 77-6037
 77-6038, 77-6203, 77-6235, 77-6236
 L E5 B666TJ A E FY&2VQ OQ -B&AEFMO, 77-6297
 L E5 B666TTT&J E FQ F1UU1 OQ, 77-6035
 L E5 B666TTT&J E FQ GQ OQ, 77-6118
 L E5 B666TTT&J E FQ OQ, 77-6030, 77-6118, 77-6203
 77-6229, 77-6230, 77-6233
 L E6 B666J, 77-6201, 77-6202
 L E6 B666J C, 77-6200, 77-6201
 L E6 D6656 1A T&&&T&J R, 77-6099, 77-6153, 77-6194
 77-6195, 77-6196, 77-6197, 77-6198, 77-6247
 77-6258, 77-6448, 77-6451, 77-6455, 77-6459
 77-6481, 77-6490, 77-6492, 77-6493, 77-6528
 77-6553, 77-6599
 L G6 D6 B666J, 77-6013
 L545 B4 C5 D 4ABCE JTJ-/G I 2, 77-6050
 L56 FYTJ A BY&1U1Y&Y FU2U- BL6YYTJ AU1 DQ
 77-6242
 L6TJ AG BG CG DG EG FG *GAMMA, 77-6205

L6UTJ A BL/UIY&U2/ 2Q C C -T, 77-6002
 L6V DVJ, 77-6049
 L64TJ A BIUIY&U2UIY&U2OV1 C C, 77-6212, 77-6230
 L66&TJ GR DOXVQ, 77-6285
 L66J BMQ, 77-6286
 L66J BNO, 77-6286
 L66J BZ, 77-6286
 L66J CMQ, 77-6286
 L66J CNO, 77-6286
 L66J CYQIMY, 77-6241
 L66J CZ, 77-6286
 L666 B6 2AB PJ, 77-6200
 MUYZM12 &QV1, 77-6274
 NNU1 &2/1, 77-6275
 NTJ 2, 77-6549
 ONN1&VM1, 77-6002
 ONN1&VN1&1, 77-6002
 ONN1&VO2, 77-6284
 ONN1&V2, 77-6284
 ONN1&1, 77-6009, 77-6063, 77-6064, 77-6065, 77-6069
 77-6254, 77-6255, 77-6256, 77-6257, 77-6258
 77-6259, 77-6267, 77-6268, 77-6298
 ONN2&2, 77-6004, 77-6063, 77-6065, 77-6214, 77-6236
 77-6249, 77-6250, 77-6251, 77-6252, 77-6253
 77-6267
 ONN2GVM2G, 77-6281
 ONO, 77-6063, 77-6066, 77-6067, 77-6068
 ON1&UNIOV1, 77-6143
 OOO, 77-6026
 OS1&1, 77-6355
 QMR DR, 77-6147
 QR BQ, 77-6042
 QR BQ DYQIMY -L, 77-6070
 QR BR, 77-6148, 77-6150
 QR CQ, 77-6042
 QR DMV1, 77-6018
 QR DR, 77-6148, 77-6150
 QR DR DQ, 77-6148
 QR DY2& 2U, 77-6028, 77-6029, 77-6034, 77-6113, 77-6227
 77-6228, 77-6229
 QVR DQ, 77-6062
 QVYQYQVQ & 2 &621 T6NJ C1 2/XV/ &622, 77-6258
 QVYZIOV1UNN &10/11, 77-6166, 77-6167
 QVYZ1R CQ DQ -L, 77-6060
 QVYZ1R DN2G2G -L, 77-6295
 QVYZ2S2 -DL, 77-6164

QVINIVQ20 22, 77-6381
 QV1OR BG DG, 77-6052
 QV1OR BG DG EG, 77-6051, 77-6161
 QV1OYQ6, 77-6165
 QV2VMN1&1, 77-6168
 QV3, 77-6355
 QY, 77-6054
 QY6&1OVO1, 77-6165
 Q2, 77-6181, 77-6182
 Q4N4&NO, 77-6003, 77-6260, 77-6261, 77-6262
 R, 77-6104, 77-6125, 77-6144, 77-6145
 R BQ DR, 77-6148
 RR, 77-6148, 77-6150
 SH2Q1Q1SH, 77-6381
 SUYM1&MMYUS&MY1U1, 77-6537
 T C666 BN INJ E FZ LN1&1 &GH, 77-6306
 T C666 BO EVJ DE FE IR BVO& LE MO NE &-NA- 2
 77-6055
 T D3 B556 BN EM JV MVTJT&J GO1 H1OVZ KZ L
 77-6293, 77-6415, 77-6455
 T D36 I666 B6 2AB U EOT&&&&J, 77-6061, 77-6207
 T E3 D6 B6666 2AB U FOTT&&&&J HQ IQ, 77-6208
 T F5 C6 B655 DOV GV OO QO RUT&&TTJ LO1, 77-6058
 77-6298
 T3OJ BR, 77-6158
 T3OTJ BXGGG, 77-6204, 77-6213
 T4OVTJ, 77-6240
 T5M CNJ DVZ ENUNN1&1, 77-6295
 T5MVMV EHJ ER& ER, 77-6060
 T5MYMTJ BUS, 77-6282, 77-6283
 T5NNVT A BR& E, 77-6180
 T5NTJ ANO, 77-6065
 T5OJ BNW E- ET5N CSJ BMVH, 77-6003, 77-6138
 77-6139
 T5OV EHJ CQ DQ EYQ1Q, 77-6064, 77-6147
 T5VOVTJ, 77-6057
 T56 BM DN FN HNJ ISH, 77-6293, 77-6295
 T56 BMJ D1YZVQ -L, 77-6139, 77-6140
 T56 BMJ D1YZVQ GQ, 77-6060
 T56 BMJ D2Z GQ, 77-6247
 T56 BN DM FVM INJ, 77-6355
 T56 BN DN FMYMVJ GUM D- BT5OTJ CQ DQ E1Q
 77-6275
 T56 BN DN FNVNVJ B F H, 77-6290, 77-6291
 T56 BN DOJ CZ HG, 77-6180
 T56 BO DO CHJ G2U1, 77-6146, 77-6150

T56 BSWMVJ, 77-6059
T6MPOTJ BO BN2G2G, 77-6452
T6MVMVJ EF, 77-6293
T6MYMVJ BUS F3, 77-6226
T6N DNTJ ANO DNO, 77-6269
T6NJ C- BT5NTJ ANO, 77-6185
T6NVMVJ EE A- ET5OTJ B1Q CQ -A&C, 77-6153
 77-6367, 77-6407
T6NVMVJ E1 A- E65OTJ B1Q CQ -A&C, 77-6153, 77-6353
 77-6370
T6VMMVJ, 77-6184
T6VMVMV FHJ F2 FR, 77-6004, 77-6009, 77-6198, 77-6212
 77-6258
T6VMVNV FHJ D F F- AL6UTJ, 77-6180
T6VMVTJ E1YQ- BL6VTJ D F, 77-6291, 77-6367, 77-6588
T66 BM DN FN HNJ IS- ET5N ONJ DNW, 77-6215
T66 BNJ BO ENW, 77-6273, 77-6287, 77-6288
T66 BOVJ, 77-6180
VH1U1, 77-6214
VH1YQYQYQ1Q -BAA -D, 77-6307
WNMYUM&N1&NO, 77-6005, 77-6067, 77-6272, 77-6287
WS1&O1, 77-6005, 77-6254, 77-6257
ZN1&1, 77-6170, 77-6171, 77-6184
ZQ, 77-6273
ZR B DNUNR B, 77-6013
ZR BR, 77-6138

ZR DR, 77-6147, 77-6286
ZVMQ, 77-6288
ZVN2&NO, 77-6273, 77-6069, 77-6267, 77-6279, 77-6280
 77-6491
ZVN4&NO, 77-6002
ZVO2, 77-6162, 77-6163, 77-6267
ZVR BQ, 77-6204
ZV1&NO, 77-6002, 77-6069, 77-6215, 77-6234, 77-6254
 77-6267, 77-6273, 77-6276, 77-6277, 77-6278
 77-6284
ZYUS, 77-6132, 77-6133
Z1CN, 77-6254
1MM1, 77-6121, 77-6169, 77-6298, 77-6566
1N1&R DNUNR, 77-6456
1N1&R DNUNR C, 77-6136, 77-6494
1UYG1U1, 77-6159
1U2R DO1, 77-6146
1X&&R BQ E CX, 77-6162
1Y&MVR D1MM1 &GH, 77-6295
2N2&YUS&S 2, 77-6212
2OV1U1VO2, 77-6204
3XR&R&VO2N2&2 &GH, 77-6258

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CARCINOGENESIS ABSTRACTS

VOLUME 15,
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И. И. СОКОЛОВА
И. И. СОКОЛОВА

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EDITOR

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COLLEGE OF MEDICINE AND DENTISTRY
OF NEW JERSEY, NEWARK

ASSOCIATE EDITOR

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RUTHANN E. AUCHINLECK, *Managing Editor*

The Franklin Research Center
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VOLUME 15, ISSUE 12

CONTENTS

	Cross Reference Abbreviations	Article Numbers	Page
REVIEW	(Rev)	77-6601-77-6666.	2333
CHEMICAL CARCINOGENESIS	(Chem)	77-6667-77-6877.	2346
PHYSICAL CARCINOGENESIS	(Phys)	77-6878-77-6914.	2397
VIRAL CARCINOGENESIS'	(Viral)	77-6915-77-7029.	2406
IMMUNOLOGY	(Immun)	77-7030-77-7091.	2435
PATHOGENESIS	(Path)	77-7092-77-7147.	2452
EPIDEMIOLOGY AND BIOMETRY	(Epid-Biom)	77-7148-77-7175.	2464
MISCELLANEOUS	(Misc)	77-7176-77-7200.	2471
AUTHOR INDEX			2477
SUBJECT INDEX			2487
CHEMICAL ABSTRACTS SERVICE REGISTRY NUMBER INDEX			2565
WISWESSER LINE NOTATION INDEX			2569

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ABBREVIATIONS

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LANGUAGE of the article is indicated in parentheses after the title and is represented by a three-letter code. The source for these codes is *MARC Manuals Used by the Library of Congress*, pages 183-187.

ABBREVIATIONS used in abstracts:

A	angstrom(s)	mOsm	milliosmolar
ACTH	adrenocorticotrophic hormone	max	maximum
ADP	adenosine diphosphate	mEq	milliequivalent(s)
AMP	adenosine monophosphate	min	minute(s)
ATP	adenosine triphosphate	ml	milliliter(s)
approx	approximately	μl	microliter(s)
av	average	mm	millimeter(s)
BCG	bacillus Calmette-Guerin	mo	month(s)
bid	twice daily	mol wt	molecular weight
C	degree(s) centigrade	N	normal concentration
cal	calorie(s)	NAD	nicotinamide adenine dinucleotide
kcal	kilocalorie(s)	NADH	reduced nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADP	nicotinamide adenine dinucleotidephosphate
Ci	curie(s)	NADPH	reduced nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NCI	National Cancer Institute
μCi	microcurie(s)	NIH	National Institutes of Health
cm	centimeter(s)	PAS	periodic acid-Schiff
CNS	central nervous system	po	orally
cpm	counts per minute	ppb	parts per billion
DNA	deoxyribonucleic acid	ppm	parts per million
ED ₅₀	median effective dose	qid	four times daily
EDTA	ethylenediamine tetraacetic acid	qod	every other day
g	gram(s)	QO ₂	oxygen quotient
kg	kilogram(s)	R	roentgen
mg	milligram(s)	RBC	red blood cells (erythrocytes)
μg	microgram(s)	RNA	ribonucleic acid
Hb	hemoglobin	rpm	revolutions per minute
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
id	intra-dermal	SGOT	serum glutamic-oxaloacetic transaminase
IgA	Immunoglobulin A	SGPT	serum glutamic-pyruvic transaminase
IgB	Immunoglobulin B	soln	solution
IgG	Immunoglobulin G	TCD	tissue culture dose
IgM	Immunoglobulin M	TCD ₅₀	median tissue culture dose
ILS	increased life span	tid	three times daily
im	intramuscular	UV	ultraviolet
ip	intra-peritoneal	WBC	white blood cells (leukocytes)
IU	International Unit(s)	wk	week(s)
iv	intravenous	wt	weight
Km	Michaelis constant	X	times
LD	lethal dose	yr	year(s)
LD ₅₀	median lethal dose		
M	molar		
μM	micromolar		

REVIEW

- 77-6601 **Validity and Limitations of Long-Term Experimentation in Cancer Research.** (Eng) Tomatis, L. (Unit Chemical Carcinogenesis, International Agency Res. Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 2, France). *IARC Sci Publ* (16): 299-307; 1977.

The contribution of long-term experimentation to the detection of carcinogenic agents is considered. There is evidence in experimental carcinogenesis that, following chronic exposure, tumor incidence and induction time are dose-related. An acceptable exposure level would be a dose that one could assume would not produce cancer within the life span of the exposed individuals. One example of the contribution of animal experimentation to the prevention of human cancer is the case of acetylaminofluorene, which was ready to be marketed on a wide scale as an insecticide when it was withdrawn because one experiment had shown it to be carcinogenic. A large number of food additives, pesticides, and herbicides have been reviewed with regard to their toxicity during the past 15 yr, and for a number of them the experimental evidence of carcinogenicity was sufficient to recommend a zero tolerance in food. This extrapolation from experimental data to man has not been widely applied occupationally, as evidenced by the aromatic amines, bis(chloromethyl)ether, vinyl chloride, vinylidene chloride, and 2-chlorobutadiene (neoprene). (31 refs.)

- 77-6602 **Extrapolation of Animal Data in Carcinogenesis to Man.** (Eng) Shubik, P. (Eppley Inst. Res. Cancer, Univ. Nebraska Coll. Medicine, 42nd and Dewey Ave., Omaha, NB 68105). *IARC Sci Publ* (16): 287-297; 1977.

The extrapolation of carcinogenesis data from man to animals and from animals to man is considered. The extrapolation of clinical observations in man to laboratory animals was an early part of the chemical carcinogenicity investigations of coal tars, cigarette smoke, and diethylstilbestrol (DES). However, tests of coal tar fractions in rabbits and mice, in an effort to develop a model of coal-tar-induced human tumors, gave different results, posing a difficult problem for the extrapolation of these data back to man. There seems to be an inverse correlation between human and animal studies of the skin application of tobacco tar condensates. Studies involving promotion effects make the extrapolation even more difficult to understand. In the case of cigarette smoking, the extrapolation from man to animals is still not entirely satisfactory. Animal studies on DES correlate remarkably well

with human clinical observations, and rodents seem adequate for investigating the effects of this chemical. It is suggested that current practices in the evaluation of chemical carcinogenicity for humans based on animal studies be reexamined. (31 refs.)

- 77-6603 **Releasing Carcinogenesis Test Results: Timing and Extent of Reporting.** (Eng) Saffiotti, U. (Experimental Pathology Branch, Carcinogenesis Program, NCI, Building 37, Room 3A19, NIH, Bethesda, MD 20014); Page, N. P. *Med Pediatr Oncol* 3(2): 159-167; 1977.

The protocol to be used for the release of carcinogenicity data from NCI is described. To meet differing requirements with respect to timing and extent of reporting, reports should be issued (when the findings are clearly identified and well-documented) in the following forms: (1) reports of preliminary findings when the evidence of carcinogenicity is strongly suggestive; (2) summary reports of completed bioassays; (3) detailed technical reports. The protocol for the release of information, applicable to all bioassay results whether positive or negative, includes the following steps: (1) preparation of a report based on sound evidence after proper scientific review of the findings; (2) delivery of the report to appropriate Federal officials; (3) release of this report through announcement in the Federal Register; (4) preparation of a press release outlining the nature of the report. (8 refs.)

- 77-6604 **Suggested Procedures for Reducing the Pathology Workload in a Carcinogen Bioassay Program, Part I.** (Eng) Fears, T. R. (Field Studies and Statistics Program, NCI, NIH, Bethesda, MD 20014); Douglas, J. F. *J Environ Pathol Toxicol* 1(1): 125-137; 1977.

Large test programs have been set up to assess the carcinogenic potential of environmental chemicals. Most test protocols require large numbers of animals and extensive pathologic evaluation of all test and control animals. Modifications to the present pathology protocol are described that will reduce the pathology workload of the program and make only small changes in the operational character of the screen. The first modification derives from the fact that a tumorigenic effect may be ruled out by looking at treated animals only. In the second procedure, simple random samples are used to provide information about the treated groups with still less pathology work. (3 refs.)

- 77-6605 **Carcinogenic Risk Assessment.** (Eng) Cornfield, J. (George Washington Univ., Washington, DC 20052). *Science* 198(4318): 693-699; 1977.

The assessment of carcinogenic risk involves statistical, scientific, and public policy considerations. Concepts in current use, such as "no observed effect levels" and "virtual safety", and the problems in implementing them by dose-response models, particularly the probit-log dose and linear models, are reviewed. The upper limits to risk provided by some conservative procedures are inconsistent with coherent balancing of risks and benefits. A common basis to the dose-response curves describing both carcinogenic and noncarcinogenic effects is found in deactivating reactions. A simplified model in which a toxic substance is activated and deactivated in separate and simultaneous reactions is presented, and the dose-response curve implied by the model is deduced. This curve has the general form of a hockey stick, with the striking part flat or nearly flat until the dose administered saturates the deactivation system, after which the probability of a response rises rapidly. This curve describes the Bryan-Shimkin methylcholanthrene-tumor incidence dose-response curve as well as the probit log-dose model. The concept of a saturation dose is relevant to risk assessments for both carcinogenic and noncarcinogenic substances. (32 refs.)

- 77-6606 **Mechanisms of Carcinogenesis: Dose Response.** (Eng) Gehring, P. J. (Toxicology Res. Lab., Dow Chemical Co., Midland, MI 48670); Blau, G. E. *J Environ Pathol Toxicol* 1(1): 163-179; 1977.

Various arguments for and against the dose-response concept of chemical carcinogenesis are reviewed. This is followed by a report of a chemical process model for carcinogenesis whose development is based on the generally accepted evidence that the carcinogenicity of many chemicals can be related to electrophilic alkylation of DNA. Using this model, some incidence of cancer, albeit negligible, will be predicted, regardless how low the dose. However, the model reveals that the cancer incidence induced by real-life exposures is likely to be greatly overestimated by currently used stochastic statistical extrapolations. Even more important, modeling of the chemical processes involved in the fate of a carcinogenic chemical in the body reveals experimental approaches to elucidating the mechanism(s) of carcinogenesis and, ultimately, a more scientifically sound basis for assessing the hazard of low-level exposure to a chemical carcinogen. (27 refs.)

- 77-6607 **Mutagenicity Tests in Chemical Carcinogenesis.** (Eng) Bartsch, H. (Unit of Chemical Carcinogenesis, International Agency for Research on Cancer,

150 cours Albert Thomas, 69008 Lyon France.). In: *Environmental Pollution and Carcinogenic Risks*. (Lyon: International Agency for Research on Cancer): IARC Scientific Publications No. 13, INSERM Symposia Series, vol. 52, pp. 229-240; 1976.

The use of mutagenicity tests in the assessment of chemical carcinogenicity is assessed. The validity of this application is demonstrated with the vinyl chloride experiments in rats, mice, human liver, and *Salmonella typhimurium* and the N-nitrosamine activities in rats, human liver, and *S. typhimurium*. The usefulness of mutagenicity tests in predicting possible carcinogenic effects of chemicals in man is valid only if the short-term bioassay is corroborated by data from long-term tests in experimental animals and is then taken together with epidemiologic studies. Mutagenicity tests, therefore, although effective in predicting the carcinogenic potential of chemicals, are not able to indicate organ and species specificity of the carcinogenic activity of the chemical or correlate mutagenic potency with carcinogenic potency. (50 refs.)

- 77-6608 **Induction of Malignant Transformation and Mutagenesis in Cell Cultures by Cancer Chemotherapeutic Agents.** (Eng) Marquardt, H. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Marquardt, H. *Cancer [Suppl]* 40(4): 1930-1934; 1977.

Data on malignant transformation and mutagenesis in vitro by cancer chemotherapeutic agents are reviewed. Uracil mustard, methotrexate, 5-fluorouracil, fluorodeoxyuridine, cytosine arabinoside, actinomycin D, Daunomycin, adriamycin, bleomycin, hydroxyurea and urethan have caused malignant transformation in vitro; some of these drugs are mutagenic along with several other therapeutic alkylating agents, antimetabolites and antibiotics. (44 refs.)

- 77-6609 **Carcinogenic Action of Anticancer Drugs with Special Reference to Immunosuppression.** (Eng) Schmahl, D. (Deutsches Krebsforschungszentrum, Institut für Toxikologie und Chemotherapie, DKFZ-Heidelberg 1, Postfach 101949, W. Germany). *Cancer [Suppl]* 40(4): 1927-1929; 1977.

Since alkylating cytostatics have been shown to be carcinogenic and antimetabolites and alkaloids have not, the immunosuppressive effects of these classes of anticancer drugs have been investigated. No parallel between carcinogenic activity and immunosuppressive property has been found. Furthermore, no connection between the immune status of the host and chemical carcinogenesis could be demonstrated. (22 refs.)

- 77-6610 Chromosomal Damage by Alcohol In Vitro and In Vivo.** (Eng) Obe, G. (Institut für Genetik, Freie Universität Berlin, D 1000 Berlin 33, Arnimallee 5-7, W. Germany); Ristow, H. J.; Herha, J. *Adv Exp Med Biol* 85A: 47-70; 1977.

Alcohol has no damaging effects on human chromosomes in vitro. The chromosomes of alcoholics, however, show a significant increase in aberrations, particularly exchange-type ones. Alcohol inhibits cellular and cell-free RNA synthesis. One possible reason for the mutagenic activity of alcohol in vivo may be an inhibition of cellular repair. (73 refs.)

- 77-6611 Role of Dietary Factors in the Endogenous Synthesis of Carcinogenic N-Nitroso Compounds (A Review).** (Rus) Rubenchik, B. L. (Lab. Carcinogenic Dietary Factors, Kiev Scientific Res. Inst. Food Hygiene, Ministry Public Health Ukrainian SSR, Kiev, USSR). *Vopr Pitan* (3): 68-75; 1977.

A review of the literature shows the ubiquitous occurrence of precursors of carcinogenic N-nitroso compounds (nitrates, nitrites and biogenic amines) in the human diet and drinking water. They are sometimes present in sufficiently large amounts for the endogenous synthesis of carcinogenic N-nitroso compounds. In many cases, the formation of carcinogenic nitrosamines from nitrites, nitrates, amines present in food, or biogenic amines in the animal body can be regarded as a fact. The nitrosation reaction that takes place in the stomach depends on factors such as the pH of the medium, the basicity of the amines, microflora, and the presence of catalysts (thiocyanate) and inhibitors (ascorbic acid). Nitrosation is most intense in an acid medium and in the presence of amines of low basicity. The bacteria that reduce nitrates to nitrites also catalyze the formation of nitrosamines in vitro. Nitrates in human and animal urine can be converted into nitrites in the urinary bladder infected by *Escherichia coli*, *Proteus mirabilis*, etc. The nitrites thus formed react with dimethylamine, piperidine, or pyrrolidine, which are metabolites of these microorganisms. The hazards of precursors of carcinogenic N-nitroso compounds are also indicated by epidemiological data showing an increased incidence of gastric cancer in areas with increased nitrate levels in the drinking water. (41 refs.)

- 77-6612 Naturally Occurring Toxic Substances in Foods.** (Eng) Gross, R. L. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, E18-613, Cambridge, MA 02139); Newberne, P. M. *Clin Pharmacol Ther* 22(5,part 2): 680-698; 1977.

Various chemical substances that occur naturally, some as a result of contamination or handling of food, are discussed, including plant toxins, nitrosamines and protease inhibitors.

Although these substances generally occur in low quantities, with little evidence for direct effects in humans, this review attempts to evaluate the hazard for man based on animal and human epidemiologic data. (89 refs.)

- 77-6613 Lead, Health Food, and Leukemia (2 Letters to Editor).** (Eng) Schwarz, K. (Lab. Experimental Metabolic Diseases, Veterans Admin. Hosp., Long Beach, CA); Crosby, W. H. *JAMA* 238(21): 2262-2263; 1977.

A preliminary diagnosis of lead poisoning in a leukemic patient was verified by urinary excretion of 0.25 mg of lead in 24 hr. The highest content of lead in any of the health food supplements ingested was 60 ppm. Lead is not known to be leukemogenic. (2 refs.)

- 77-6614 Nutrition and Drug-metabolizing Enzymes.** (Eng) Campbell, T. C. (Div. Nutritional Biochemistry, Cornell Univ., Ithaca, NY 14853). *Clin Pharmacol Ther* 22(5,part 2): 699-706; 1977.

In livers of male Sprague-Dawley rats fed a protein deficient diet, cells were larger, fewer per liver wt, and had a higher lipid content and less microsomal protein than in control livers. The protein-deficient diets depressed the binding of aflatoxin B₁ to DNA by 70%, possibly by decreasing mixed-function oxidase activity. Other data on the relationship between nutrition, carcinogenic susceptibility, and pharmacological response are reviewed. (33 refs.)

- 77-6615 Genital Tract Anomalies and Cancer in Females Exposed In Utero to Diethylstilbestrol. Brief Report on the DESAD Project.** (Eng) Sestili, M. A. (NCI, Div. Cancer Control and Rehabilitation, Blair Building, Room 617, Bethesda, MD 20014). *Public Health Rep* 92(5): 481-484; 1977.

The information in the 1977 DESAD (DES-Adenosis) project report on genital tract anomalies and cancer in women exposed in utero to diethylstilbestrol (DES) or DES-like drugs is reviewed briefly. The DES-type drugs that may have been prescribed to pregnant women are tabulated. Populations at risk are defined along with six protocol aims of the project. (14 refs.)

- 77-6616 Estrogens and Endometrial Cancer.** (Eng) Anonymous (No affiliation given). *Behav Neuropsychiatry* 8(1/12): 39-41; 1977.

Three recent studies on estrogen use in postmenopausal wom-

en indicate that there is an increased risk of endometrial cancer (4 to 8/1,000 women) for those who take estrogen preparations. This increase is highly significant, since the annual incidence of endometrial cancer in postmenopausal women had been estimated to be 1/1,000. The Food and Drug Administration recommends following treatment regimen as the least hazardous: cyclic administration of the lowest effective dose for the shortest possible time, with monitoring for endometrial cancer. (11 refs.)

- 77-6617 **Experimental Basis for Multiple Primary Carcinogenesis by Sex Hormones. A Review.** (Eng) Lemon, H. M. (Dept. Internal Medicine, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB 68105). *Cancer [Suppl]* 40(4): 1825-1832; 1977.

A review of experimental data and clinical cases indicates that multiple tumors may develop through the incorporation of sex hormones into receptor protein complexes in the target tissue; these complexes stimulate further synthesis of receptor protein, and eventually hyperplasia results. Receptor protein-hormone complexes may be transferred from neoplastic to adjacent hormone independent tissues (eg, muscle or lymphatic). Estrogens may also act as co-carcinogens in breast cancer. (50 refs.)

- 77-6618 **Estriol and Prevention of Mammary Carcinoma.** (Eng) Lemon, H. M. (Univ. Nebraska Medical Center, Omaha, NB 68105). *Cancer Detect Prevent* 1(2): 263-281; 1976.

In this review, evidence is given to support the concept that sustained elevation of estriol in the body fluids of mammals produces a castrationlike effect on breast tissues by displacing estradiol from steroid-receptor protein complexes, thereby greatly reducing the cocarcinogenic effect of estradiol in these tissues. In this latter respect, estriol has been shown to prevent up to 90% of chemically induced breast carcinomas in rats during their natural life span. Discussion is made of epidemiological indications of the role of estriol in accounting for the geographic, ovarian, and pregnancy factors reducing mammary carcinoma risk; the possibility that estriol is responsible for the protective effect of early pregnancy on breast cancer risk; castration inhibition of breast carcinogenesis; the binding affinity of mammary estrogen receptors for steroids in extracellular fluids; estriol therapy of pre- and postmenopausal women; and the role of estriol in preventing endometrial cancer. (67 refs.)

- 77-6619 **Involvement of Prolactin in Carcinogenesis and Growth of Mammary Gland Tumors in Animals**

and Humans. (Rus) El'tsina, N. V. (Moscow, USSR). *Vopr. Onkol* 22(12): 81-91; 1976.

Current data on the role of prolactin in the differentiation of mammary gland epithelium are summarized. When rats with 7,12-dimethylbenz(a)anthracene-induced mammary gland carcinomas were treated with compounds that inhibit prolactin secretion, the number of tumors decreased by 50%. On the other hand, 50% of the animals with prolactin hypersecretion developed spontaneous mammary gland tumors compared to 19% of the controls. Inhibitors of prolactin secretion were used to treat patients with breast cancer. Of 15 patients with disseminated metastases to the bones treated with L-dopa (1.5-3 g/day, 4x/day, po), 2 had complete and 10 had partial pain relief. Of six patients with skin metastases two showed significant tumor regression. (77 refs.)

- 77-6620 **Oral Contraceptives and Breast Neoplasia.** (Eng) Cole, P. T. (Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA 02115). *Cancer [Suppl]* 39(4): 1906-1908; 1977.

Studies on the relationship between oral contraceptive (OC) use and the development of benign and malignant breast disease are reviewed. Studies have shown a moderate (20%) reduction in risk of benign breast conditions for users of OCs. It also appears that the protective effect of OCs persists for several years following cessation of use. The risk of breast cancer seems to be either not altered or slightly diminished by OC use. However, among women who have benign breast disease, the risk of malignancy is strikingly elevated by OC use. Another study found that the use of exogenous estrogen for treatment of menopausal symptoms increases the risk of both benign and malignant conditions, but especially increases the risk of cancer among women who develop the benign condition. A concept of two types of benign breast disease, only one of which is premalignant, has been developed. It is speculated that while OCs reduce the frequency of the nonpremalignant lesion, both OCs and therapeutic estrogens increase the frequency of the premalignant lesion. (1 refs.)

- 77-6621 **Liver Tumors Developing During Contraceptive and Anabolic Drug Therapy.** (Ger) Scheuer, A. (Medizinische Universitätsklinik, E. Mannkopffstrasse 1, D-3550 Marburg/Lahn, W. Germany); Lehmann, F. G. *Internist* 18(4): 208-214; 1977.

A review of the literature showed that between 1973 and 1976, 37 hepatocellular adenomas, 19 focal nodular hyperplasias, and 8 hamartomas developed in patients taking oral contraceptives. The livers of most patients showed distinctive vascularization, some with developing small hemorrhagic areas. Eleven cases of hepatocellular carcinoma also occurred.

curred, 1 being diagnosed during pregnancy. The symptoms of the carcinoma patients were similar to those of older patients with the same disease. Clinically, the benign liver tumors caused acute abdominal pain due to tumor rupture and hemoperitoneum, usually in the right upper quadrant. The tumors were palpable or were discovered at laparotomy. The development of abdominal symptoms in young women should lead to a differential diagnosis of possible liver tumors in relation to contraceptive use. A causal relationship between anabolic drugs and hepatocellular adenoma and focal nodular hyperplasia has not yet been established, but the number of peliosis hepatis cases associated with androgen therapy is sizable, and a causal relationship must be inferred here. (97 refs.)

- 77-6622 **Liver Tumors Due to Environmental Factors.** (Ger) Popper, H. (Mount Sinai Sch. Medicine, Stratton Lab. Study Liver Disease, Fifth Ave. and 100th St., New York, NY 10029). *Internist* 18(4): 182-187; 1977.

The histology and morphology of liver fibrosis and angiosarcoma due to long-term occupational exposure to vinyl chloride, inorganic arsenic, and thorium dioxide are reviewed along with the effect of anabolic steroids and oral contraceptives on hepatocellular adenomas and carcinomas. Reference is made to experiments with mice and rats. (56 refs.)

- 77-6623 **Angiosarcoma of the Liver in Great Britain** (2 Letters to Editor). (Eng) Smith, P. M. (Welsh Natl. Sch. Medicine, Penarth, Glamorgan, Wales); Williams, D. M.; Dalderup, L. M. *Br Med J* 2(6095): 1149-1150; 1977.

Only two cases of angiosarcoma of the liver following vinyl chloride exposure have been noted in Great Britain. In comparison, noncirrhotic portal fibrosis is commoner and therefore of greater importance. In the Netherlands, 27 cases diagnosed as angiosarcoma were reviewed, and only 9 were found to be definite. None of the nine patients had any contact with vinyl chloride, but one had been on long-term arsenic medication. (6 refs.)

- 77-6624 **An Overview of the Vinyl Chloride Hazard in Canada.** (Eng) Basuk, J. (Science Council Canada, Ottawa, Canada); Nichols, A. *Chem Can* 29(7): 24-38; 1977.

The effects of occupational exposure to vinyl chloride monomer (VCM) are emphasized in this review, which also includes a discussion of the properties and processing of VCM. VCM came to attention as a health hazard in 1973, when three cases of a rare form of liver cancer, angiosarcoma, were

reported in workers from a VCM factory. Since then, 48 victims have been identified; others who may have died from angiosarcoma are unknown because of difficulty in diagnosing the disease. VCM has chronic effects on human beings at high levels of exposure. It causes a specific occupational disease known as acroosteolysis, in which there is both Raynaud's syndrome and sclerodermiform lesions. In animal studies VCM has produced a wide range of tumors in rats, mice, and hamsters: Zymbal gland carcinomas, nephroblastomas, angiomas and angiosarcomas of the liver and other sites, trichoeplitheliomas, hepatomas, lung adenomas, mammary adenomas and carcinomas, and lymphomas. Recent findings suggest that mammary carcinomas can be induced in laboratory animals at concentrations of ≤ 1 ppm. Efforts to control the adverse health effects of VCM include the setting of standards for occupational exposure to VCM, improved manufacturing techniques to minimize VCM exposure and residual VCM in polyvinyl chloride resin, and increased research on the epidemiology of VCM-related diseases and on diagnosing preangiosarcoma tumors. (65 refs.)

- 77-6625 **Surveillance of Spontaneous Abortions. Power in Environmental Monitoring.** (Eng) Kline, J. (Columbia Univ. Coll. Physicians and Surgeons, New York, NY 10032); Stein, Z.; Strobino, B.; Susser, M.; Warburton, D. *Am J Epidemiol* 106(5): 345-350; 1977.

The advantages of using spontaneous abortions, rather than birth defects, to monitor environmental teratogens are discussed. Theoretically, a change in the incidence of spontaneous abortions or of anomalies in spontaneous abortions should be detectable 6 mo or more before a change in the incidence of birth defects. Moreover, teratogens that cause many anomalies cannot be detected by studies of birth defects since the majority of anomalous conceptions lead to spontaneous abortions. Abortion specimens can also be preserved for future studies. The spontaneous abortion approach is illustrated by the potential teratogenic effects of paternal exposure to vinyl chloride (VC). VC may affect male germ cells by causing chromosome breaks, dominant or recessive lethal mutations, and/or chromosome abnormalities. Morphologic and karyotype analyses of a sample series of spontaneous abortions are discussed. (14 refs.)

- 77-6626 **The Less Harmful Cigarette.** (Eng) Workshop on Lung Cancer (Geneva, Switzerland). In: *Lung Cancer. A Series of Workshops on the Biology of Human Cancer.* Wynder, E. L.; Hecht, S., eds. (Geneva: International Union Against Cancer): Vol 25(3), pp 131-154; 1977.

The characteristics of cigarette smoke and a review of the carcinogenicity of both the smoke and its condensate are presented. Methods of making a cigarette less harmful include

culturing and curing tobacco to select for low concentrations of hazardous components, use of additives to minimize tobacco content, removal of nicotine, construction of cigarettes with high porosity paper, use of smoke dilution devices, and the use of filters. (99 refs.)

- 77-6627 **Asbestos Exposure--Its Related Disorders.** (Eng) Constantinidis, K. (Medical Res. Council, Pneumoconiosis Unit, Penarth, Glamorgan, Wales). *Br J Clin Pract* 31(7/8): 89-101; 1977.

Exposure to asbestos can result in asbestosis, lung cancer and mesothelioma of the pleura. People with asbestosis are more susceptible to the development of lung cancer than healthy persons; and some studies suggest that exposure to asbestos, even without subsequent asbestosis, increases the risk of bronchial carcinoma. Cigarette smoking and asbestosis have an additive carcinogenic effect. Mesothelioma of the pleura can result from exposure to small amounts of asbestos; the latent period is > 20 yr. Clinical and histological features of these disorders are presented. (91 refs.)

- 77-6628 **Asbestos Cancers as an Example of the Problem of Comparative Risks.** (Eng) Gilson, J. C. (MRC Pneumoconiosis Unit, Llandough Hosp. Pengarth, Glamorgan, CF6 1XW, Wales). In: *Environmental Pollution and Carcinogenic Risks*. (Lyon: International Agency for Research on Cancer): IARC Scientific Publications No. 13, INSERM Symposia Series vol. 52, pp. 107-116; 1976.

The carcinogenic effects of asbestos, particularly the production of mesotheliomas and bronchial cancers, are thought to be related to the particle shape, size, and composition. The order of risk from different fiber types is crocidolite > amosite > chrysotile > anthophyllite. Evidence so far indicates that these types of asbestos are less carcinogenic than natural fibrous minerals. Figures from the chrysotile mining and milling industries in Quebec suggest that there is a dose-response relationship, although lightly exposed groups (ie, the general population) are at negligible risk. Within the industry those working in insulation show highest risk. However, the risk of cancer in smoking asbestos workers is greater than in those who do not smoke. Asbestos-induced cancers at sites other than in the lungs are relatively small, with the gastrointestinal neoplasms being most frequent. Experimental and epidemiologic evidence could be used to predict safe doses based on the physical and chemical properties of natural and man-made fibers. (24 refs.)

- 77-6629 **Animal Models.** (Eng) Workshop on Lung Cancer (Geneva, Switzerland). In: *Lung Cancer. A Series of Workshops on the Biology of Human Cancer*. Wynd-

er, E. L.; Hecht, S., eds. (Geneva: International Union Against Cancer): Vol 25(3), pp. 81-130; 1977.

A review of lung carcinogenesis induced by chemical and physical carcinogens in the most commonly used animal models -- mouse, rat, hamster (Chinese, Syrian, European) and dog -- is presented. Few data are available on lung cancer in monkeys; those that are susceptible to tumor induction by polycyclic hydrocarbons are also susceptible to viral oncogenesis. A review of the pros and cons of each animal test system indicates that the European hamster provides the best model available for respiratory tract carcinogenesis. (31 refs.)

- 77-6630 **Occupational Exposure to Radiation as a Cancer Hazard.** (Eng) Archer, V. E. (Natl. Inst. Occupational Safety and Health, Salt Lake City, UT 84108). *Cancer [Suppl]* 39(4): 1802-1806; 1977.

It has been hypothesized that ionizing radiation causes cancer by activating a single-point mutation or a series of somatic mutations. In a 25-yr study, uranium miners were found to have a high incidence of lung cancer resulting from exposure to internal α radiation from inhaled dust carrying radioactive daughter products. This incidence was increased further by cigarette smoking. In addition, persons working in uranium processing plants have an increased incidence of lymphoma and lung cancer, and radium-dial painters have an excess of osteosarcomas caused by α radiation deposited in bone. Early roentgenologists developed an excess of leukemias, where multiple myelomas are elevated in those beginning practice more recently. Assuming that the dose-response curves are linear, the relative increase in the risk of radiation-induced cancer is in the range of 0.2% to 6%/yr/rem (radiation equivalent-man)/million adults exposed. Most radiation induced cancers can be identified only by epidemiologic methods. Several other factors may act synergistically with the radiation. (47 refs.)

- 77-6631 **I. Biological Implications of Radiation.** (Eng) Bond, V. P. (Dept. Life Sciences, Brookhaven Natl. Lab., Associated Univs., Incorporated, Upton, NY). *Rhode Isl Med J* 60(10): 467-473; 1977.

The biological effects of radiation on the body are reviewed and related to exposure from nuclear power plants. Dividing cells are more sensitive to radiation. Since the bone marrow contains cells that are constantly dividing, the effects of large radiation doses on these cells become apparent in the peripheral blood within days of exposure. The effects are similar to those of aplastic anemia and, specifically, the problems that result from an aplastic marrow. However, if small doses are given over large periods of time, no harm may result. Anyone who recovers from a large dose of radiation always

has a small probability that late effects will be manifested. This is shown by the incidence of leukemia in radiation-exposed persons in Japan. The dose at the edge of a nuclear reactor site is 5 milli-rems (radiation-equivalent-man)/yr, but it falls by a factor of 1,000 over a radius of 50 miles. When these doses are compared with background doses, exposure would result in < 1 additional case of cancer per year for the entire US; ie, no detectable effect would result. The relative risk of death for different phases of coal, nuclear, oil, and natural gas power generation are reviewed, and the risk of injury or death from nuclear exposure is compared to the risk from other accidental incidents. (1 ref.)

- 77-6632 **Radiation Hazard--Experience with Therapeutic and Diagnostic ^{131}I .** (Eng) Dobyns, B. M. (Case Western Reserve Univ., Sch. Medicine, Cleveland, OH 44108). In: *Radiation-associated Thyroid Carcinoma*. DeGroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): 539 pp.; 459-483pp.; 1977.

The incidence of thyroid neoplasms following therapeutic or diagnostic ^{131}I treatment was investigated based on a survey of 35,568 cases from the records of 26 medical centers. Of 34,684 patients treated for hyperthyroidism, 96 developed malignant lesions, 10 of which had been removed before entry into the study. Of the remaining 86, 70 were found among > 30,000 patients with Graves' disease, 9/2,700 with toxic adenomas, and 7/1,600 with unclassified hyperthyroidism. The incidence rate was 2.3/1,000 for Graves's disease, 3.3/1,000 for toxic adenomas, and 4.3/1,000 for unclassified adenomas. There was an incidence of only 0.41/1,000 among patients with hyperthyroidism and concurrent thyroid neoplasms and 0.88/1,000 in patients with subsequently occurring carcinomas. Only two patients treated with x-ray therapy were found to have a thyroid neoplasm, and one of these had also received ^{131}I treatment. The difference in latent period, age at therapy, types of lesions, and other factors are outlined. Since very few children and no normal subjects were treated and the observation period was inadequate, it was difficult to estimate any tumorigenic effect. (11 refs.)

- 77-6633 **Epidemiology of Thyroid Cancer--Part II.** (Eng) Schottenfeld, D. (No affiliation given); Gershman, S. T. *Clin Bull* 7(3): 98-104; 1977.

A review is presented of the role of multiple endocrine adenomatosis syndromes, iodine deficiency, Graves' disease, Hashimoto's thyroiditis, and human radiation exposure in thyroid cancer. A review of the literature in the association between thyroid and breast cancer suggested that there is no common cause for the two. (95 refs.)

- 77-6634 **The Natural History of Thyroid Cancer.** (Eng) Beierwaltes, W. H. (Dept. Medicine, Univ. Michigan, Ann Arbor, MI). *Radiation-associated Thyroid Carcinoma*. DeGroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): 539 pp.; pp. 63-74; 1977.

Chromosome studies of transplanted Fischer rat thyroid tumors and experience in treating patients with well-differentiated thyroid cancer are reviewed. Thyroid-stimulating hormone-induced hyperplasia may induce the chromosome changes that promote the development of metastatic thyroid carcinoma. X-rays or the γ or β radiation from ^{131}I may also induce the necessary chromosome changes. Occult thyroid cancers can regress or remain dormant; they rarely go on to clinical cancer. Adequate surgical treatment of clinical cancer below age 40 followed by ^{131}I and thyroid hormone is effective. Inadequately treated well-differentiated thyroid cancer recurs. Older persons with well-differentiated cancer may eventually die of undifferentiated thyroid cancer, for which there is no effective treatment. (23 refs.)

- 77-6635 **Pathology of Irradiation Thyroid Damage.** (Eng) Doniach, I. (Inst. Pathology, London Hosp., Whitechapel, London, England). In: *Radiation-associated Thyroid Carcinoma*. DeGroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): 539 pp.; pp. 199-211; 1977.

The two major biological effects of ionizing radiation are (1) induction of follicular cell neoplasia by x-rays at 100-2,000 rads of ip ^{131}I at 1-50 μCi and (2) follicular cell sterilization and eventual thyroid atrophy with 100 μCi ^{131}I . Postradiation neoplasia is enhanced by any regimen that stimulates thyrotropin secretion. Suppression of secretion by exogenous thyroid hormone reduces follicular cell neoplasia. Natural growth or induced hyperplasia of the thyroid after radiation may give rise to multiple tumors, as seen in a series of irradiated, hyperthyroid California children and in Marshall Islanders. (30 refs.)

- 77-6636 **On the Causes of Melanomas.** (Eng) Nordlund, J. J. (Dept. Dermatology, Yale Univ., Sch. Medicine, New Haven, CT 06510); Lerner, A. B. *Am J Pathol* 89(2): 443-448; 1977.

The role of sunlight in the etiology of melanoma is considered. Most melanoma patients are fair-skinned and do not tan, ie, do not synthesize melanin easily; sunlight stimulates melanin synthesis. Furthermore, melanomas tend to develop on sun-exposed areas of the skin. The potential of sunlight

to stimulate pigmented lesions to undergo malignant transformation is still unknown. Melanomas in the platyfish and Sinclair miniature swine are discussed. (24 refs.)

- 77-6637 **Ultraviolet Radiation and Tumor Immunity.** (Eng) Kripke, M. L. (Basic Res. Program, NCI Frederick Cancer Res. Center, Post Office Box B, Frederick, MD 21701). *J Reticuloendothel Soc* 22(3): 217-222; 1977.

Upon chronic treatment with UV light, long before primary tumors appear, mice are unable to resist the growth of UV-induced tumors implanted sc on their nonirradiated side. Mechanisms for this systemic alteration were investigated. In experiments with C3H(MTV-) mice irradiated with Westinghouse FS40 sunlamps that delivered an av dose rate of 2.8 joules/meter²/sec over a wavelength range of 280 to 340 nanometers, UV irradiation interfered with immunologic functions as a result of direct lymphocyte toxicity and/or local inhibition of cellular infiltration. UV irradiation also led to the development of suppressor cells in the lymphoid population. These cells prevented in vivo rejection against syngeneic and, probably, autochthonous, UV-induced tumors. The specificity range of the suppressor cells included the spectrum of neoantigens on the UV-transformed cells; it did not include exogenous antigens such as histocompatibility antigens. Studies with C57BL/6 mice and C3H- mice irradiated for 2 to 4 mo prior to testing indicated that UV irradiation did not decrease host resistance against all syngeneic tumors per se or even against all syngeneic fibrosarcomas. The growth of a B16 melanoma tumor was accelerated by UV irradiation. It is not known if this stimulation was mediated immunologically. (14 refs.)

- 77-6638 **D-Type Oncornavirus and Its Possible Role in Carcinogenesis.** (Rus) Ershov, F. I. (Dept. Oncogenic Viruses, D. I. Ivanovskii Inst. Virology, Acad. Medical Sciences USSR, USSR); Zhdanov, V. M. *Vopr Onkol* 23(5): 110-119; 1977.

Studies of D-type oncornavirus and its possible role in carcinogenesis are reviewed. The two types of D-type oncornavirus (simian and human) are similar but not identical, in view of their immunological characteristics and polypeptide composition. After penetration into the cell and the formation of provirus DNA, the genetic material of the virus becomes part of the cell genome. The production of D-type oncornavirus in tumor cells begins with the transcription of RNA from the integrated DNA sections. This RNA is a single-stranded 35S molecule that migrates into the cytoplasm; it becomes partially associated with proteins and is converted into spiralized fibrils. Part of the 35S RNA molecule in these fibrils is transformed into 60S RNA and other virion proteins. The latter are produced by cleavage of the large precursor protein, and they are used to form nucleoids. These nu-

cleoids are incorporated into the virion and become detached from the cell; the 60S RNA is now transformed into 70S RNA. These findings indicate the "extracellular" maturation of oncornavirus RNA in human tissue culture oncornavirus D, similar to C-type oncornavirus. The ubiquitous occurrence of human oncornaviruses among monkeys and in man, and, especially, in tumor cell cultures and cancer tissues indicates their possible role in carcinogenesis. (58 refs.)

- 77-6639 **Experimental Carcinogenesis. Induction of Multiple Tumors by Viruses.** (Eng) Sanders, F. K. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021). *Cancer [Suppl]* 40(4): 1841-1844; 1977.

Mice of known genetic composition are easily available and are susceptible to various tumors induced by injection with the DNA-containing mouse polyoma virus. The resulting tumors are transplantable and metastasizing. It is suggested that the polyoma virus/mouse host system be used to study multiple tumor induction by viruses. (19 refs.)

- 77-6640 **The Epidemiology of the Feline Leukemia Virus (FeLV).** (Eng) Hardy, W. D. (Lab. Veterinary Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021); McClelland, A. J.; MacEwen, E. G.; Hess, P. W.; Hayes, A. A.; Zuckerman, E. *Cancer [Suppl]* 39(4): 1850-1855; 1977.

Seroepidemiological studies show that feline leukemia virus (FeLV), an oncornavirus that causes case clustering of feline lymphosarcoma, is contagious in the natural environment. Several studies measuring either FeLV envelope (type-specific) antigens, FeLV internal (group-specific) antigens, or feline oncornavirus-associated cell-membrane antigen (FOCMA) in cat populations have provided conclusive evidence that FeLV is contagious. The most likely routes of transmission are through the saliva and urine. Effective control of FeLV has been accomplished by identifying and removing carrier animals from households and catteries. The development of a vaccine against FeLV is currently being investigated. At present, there is no evidence that FeLV infects humans living with FeLV-infected cats. (35 refs.)

- 77-6641 **Transmissibility of Animal Cancer Viruses (Letter to Editor).** (Eng) Essex, M. (Boston, MA 02115); Hardy, W. D. *J Am Vet Med Assoc* 171(8): 685-688; 1977.

Feline leukemia virus (FeLV)-infected cats are considered to be a potential source of infection for humans, especially un-

born fetuses and children. FeLV replicates more efficiently in human cells than chicken or cattle oncornaviruses do. Antibodies to FeLV have been detected in human sera. (14 refs.)

- 77-6642 **Viruses and the Pathogenesis of Human Leukemia.** (Eng) Gallo, R. C. (NIH, NCI, Bethesda, MD 20014). *Schweiz Med Wochenschr* 107(4): 1436-1440; 1977.

Several types of conditioned culture media contain factors which affect the growth of normal and/or leukemic myelogenous cells only, with no effect on normal marrow, blood cells or lymphocytic leukemia cells. These findings indicate that myelogenous leukemia cells are not completely autonomous. The role of RNA tumor viruses in animal leukemias is reviewed, and evidence for RNA tumor viruses in humans is presented. (13 refs.)

- 77-6643 **The Role of Epstein-Barr Virus in Human Disease.** (Ger) Schmitz, H. (Zentrum für Hygiene, Hermann-Herder-Strasse 11, D-7800 Freiburg, im Breisgau, W. Germany). *Acta Med Austriaca Special Issues*: 94-95; 1977.

Epstein-Barr virus (EBV) nucleic acid has been found in Burkitt's lymphoma, nasopharyngeal carcinoma, and some tonsillar tumors. However, there is as yet no conclusive evidence on the induction of these human tumors by EBV. (9 refs.)

- 77-6644 **Epstein-Barr Virus and Human Malignancy.** (Eng) Ziegler, J. L. (NCI, Bethesda, MD 20014); Magrath, I. T.; Gerber, P.; Levine, P. H. *Ann Int Med* 86(3): 323-336; 1977.

The association of Epstein-Barr virus (EBV) and two human malignancies, Burkitt's lymphoma and nasopharyngeal carcinoma, is reviewed. Seroepidemiologic, virologic, and immunologic evidence is summarized, and several hypotheses of the possible etiologic role of EBV in these tumors are presented. More work is needed to determine whether EBV is oncogenic for man and to ascertain the biological and clinical significance of its association with Burkitt's lymphoma and nasopharyngeal carcinoma. (153 refs.)

- 77-6645 **Factors Involved in the Development of Human Tumors Using Epstein-Barr Virus as an Example.** (Ger) Henle, W. (Div. Virology, Joseph Stokes, Jr. Res. Inst., Children's Hosp. Philadelphia, 34th St. and Civic Cen-

ter Blvd., Philadelphia, PA 19104). *Klin Wochenschr* 55: 847-855; 1977.

Proof that some viruses are oncogenic for humans can be provided only by indirect evidence based on the following criteria: (1) detection of viral antigens or viral genetic information in a given tumor; (2) transformation of normal human cells by the virus in tissue culture; (3) induction of tumors in animals by the virus; and (4) demonstration of enhanced titers of antibodies to the virus in patients bearing the tumor. Based on these criteria, there is a causal relationship between Epstein-Barr virus (EBV) and Burkitt's lymphoma and nasopharyngeal carcinoma. However, genetic, immunologic, or environmental factors must play an additional role. Although EBV causes infectious mononucleosis and is widely disseminated, virus-associated tumors are rare. (14 refs.)

- 77-6646 **Lymphoma, Immunodeficiency and the Epstein-Barr Virus.** (Eng) Rosen, F. S. (Children's Hosp. Medical Center, Boston, MA 02115). *N Engl J Med* 297(20): 1120-1121; 1977.

Development of fatal infectious mononucleosis, agammaglobulinemia, or malignant B-cell lymphoma following Epstein-Barr virus infection has been reported in males of a large kindred. This susceptibility is apparently X-linked. It is suggested that either the infection wipes out the B cell population, or the B cells undergo malignant transformation without subsequent killing by T cells. Reasons for this behavior are unknown. (4 refs.)

- 77-6647 **Tumor Immunology.** (Eng) Harris, J. (Univ. Ottawa, Faculty Medicine, Ottawa General Hosp. Ottawa, Canada). In: *Clinical Oncology*. Horton, J.; Hill, G. J., eds. (Philadelphia: W. B. Saunders Co.): pp. 192-223; 1977.

Several aspects of tumor immunology are considered. Virtually all human neoplasms have tumor-specific or tumor-associated antigens that elicit an immune response. Evidence in favor of the theory of immune surveillance as a host defense mechanism that aborts the formation of malignant growths includes the age incidence for malignant disease, the results of animal thymectomy experiments, clinical observations, the increased risk of malignancy in primary immunodeficiency states, and the association between chemical immunosuppression and malignancy. There are several ways in which tumors cells may escape detection and/or destruction by immune mechanisms, including tolerance induction, immunoselection, and blocking antibody activity. Patients with malignant disease who have the most intact cell-mediated immune function will probably have the best response to treatment. Immune function may be altered by fac-

tors other than the malignant process alone: hormones, cytotoxic drugs, radiotherapy, and certain surgical procedures will also suppress immune function. Practical information regarding a patient's immune status can be obtained from relatively simple in vivo tests such as an absolute lymphocyte and granulocyte count together with skin test studies. The immunodepression associated with hemopoietic and lymphoid malignancies results from the malignant transformation of those cells actually responsible for immune reactions. The disturbances of immune function that result have been more sharply defined and better characterized than those that occur in patients with solid tumors. (102 refs.)

- 77-6648 **Maintenance of the Resting State and Potential Regulators of the Proliferative Phase.** (Eng) Lopatin, D. E. (Dental Res. Inst., Univ. Michigan, Ann Arbor, MI 48109); Ranney, D. F. In: *Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York: Academic Press, Inc.): 825 pp.; 195-218; 1977.

Studies of a low-mol-wt suppressor (LMWS) of lymphocyte proliferation produced by cultured spleen cells and macrophages during unstimulated conditions are reviewed. The production and release of LMWS are functions of ongoing cellular metabolism and depend in part on protein synthesis. Cell proliferation is not required for LMWS release. Dose-response studies indicate that inhibition is species-independent, B and T precursors are equally affected, and spontaneously dividing thymic precursor cells are more sensitive than mature thymocytes. Comparisons of the effects of LMWS on normal and malignant lymphoid target cells suggest that malignant transformation, the self-propagation of certain lymphoid cell lines, or the proliferation of particular cell lines may require the suppression of sensitivity or susceptibility to these low-mol-wt inhibitory factors. The allogeneic and mitogenic stimulation of producing cells implicates the LMWS factor as a potential feedback regulator of lymphocyte DNA synthesis. The data suggest that the suppressive factor acts during the maturation of cells from precursors. It appears to act only on cells able to be activated by antigen. A model is presented of the LMWS role during the maturation of the immune response. The age-dependent release of LMWS and its density dependence suggest a primary role in the ontogeny of the immune response. (39 refs.)

- 77-6649 **Dysfunction of Suppressor Mechanisms Associated with Immunodeficiency and Autoimmunity.** (Eng) Waldmann, T. A. (Metabolism Branch, NCI, NIH, Bethesda, MD 20014); Broder, S.; Krakauer, R.; Durm, M.; Goldman, C.; Meade, B.; Strober, W. In: *Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York: Academic Press, Inc.): 825 pp.; 269-287; 1977.

Disorders of suppressor mechanisms associated with (1) pri-

mary immunodeficiency diseases, (2) the immunodeficiency related to malignancy, and (3) autoimmune disorders are discussed. An abnormal number or abnormal state of activation of suppressor cells affecting all immunoglobulin (Ig) classes has been demonstrated in patients with common variable hypogammaglobulinemia (HGG) and in some patients with HGG associated with a thymoma. Host suppressor cells have been shown to play a part in the polyclonal Ig deficiency of certain patients with myeloma and mice with transplantable plasmacytomas. These host suppressor cells are non-T-cell phagocytic, mononuclear cells that produce a low-mol-wt protein suppressor substance. The results are consistent with the idea that a major mechanism leading to HGG associated with myeloma is the activation of host immunoregulatory mononuclear cells that produce a suppressor protein. Loss of suppressor T-cell activity was found to be involved in the pathogenesis of autoimmune disorders in the animal models of autoimmunity of NZB/W mice. Administration of the suppressor T-cell product, the soluble immune response suppressor (SIRS), to young NZB/W mice led to a marked reduction in the manifestations of autoimmunity in these animals. SIRS has potential for the successful treatment of human diseases associated with the loss of suppressor T-cell function. (31 refs.)

- 77-6650 **Suppression of Immune Responses by Product of Activated T Cells.** (Eng) Rich, R. R. (Dept. Microbiology and Immunology, Baylor Coll. Medicine, Houston, TX 77030); Rich, S. S. In: *Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York: Academic Press, Inc.): 825 pp.; 251-268; 1977.

The characteristics of three T-cell factors that suppress immune responses are compared: (1) concanavalin A (Con A) induced soluble immune response suppressor (SIRS); (2) an antigen-induced specific suppressors of antibody synthesis; and (3) the nonspecific suppressor of mixed lymphocyte reaction (MLR) released from alloantigen-activated T cells. Each of these factors is produced by activated murine T cells and is distinguished from immunoglobulins by physicochemical properties. Although the molecular structure of these factors is unknown, they have a similar molecular size and, with the exception of SIRS, share the expression of H-2 antigenic determinants. Physicochemical studies indicate that SIRS is similar to or identical with murine migration inhibitory factor. Two antigen-induced specific suppressors of antibody synthesis are discussed. One requires H-2 complex homologies between the T-cell strain from which the factor is extracted and helper T cells that are the target of activity. MLR suppressor factor acts nonspecifically with regard to the stimulator cell strain, but it exhibits marked genetic restriction in its capacity to interact with MLR responder cells and thereby effect suppressor activity. Whether the differences among these suppressor factors reflect a genuine distinctness of the processes regulated, peculiarities of the assay system studied or a fundamental biological redundancy must be investigated. (26 refs.)

- 77-6651 **Quantitative Change of Serum Protein and Immunoglobulin in Patients with Solid Cancers.** (Eng) Lee, Y. N. (Dept. Surgery, Univ. Southern California Sch. Medicine, 1200 N. State St., Los Angeles, CA 90033). *J Surg Oncol* 9(2): 179-187; 1977.

Serum protein and immunoglobulin studies in patients with solid cancers are reviewed. The most common serum protein changes are a reduction in albumin concentration and an elevation of α globulin, especially the α -2 fraction. Serum IgG increases significantly in patients with skin or lung cancer, but it decreases in patients with breast and prostate cancer. IgM is elevated in patients with sarcoma, melanoma, or brain tumors and decreased in patients with ovarian cancer. IgA is elevated in persons with cancer of epithelial secretory organs, such as skin, breast, head and neck, lung, gut, prostate, and uterine cervix. Whether these findings reflect specific changes in the humoral immune response of the tumor host remains to be determined. (75 refs.)

- 77-6652 **Recent Studies on the Identification of Proliferative Abnormalities and of Oncogenic Potential of Cutaneous Cells in Individuals at Increased Risk of Colon Cancer.** (Eng) Kopelovich, L. (Memorial Sloan-Kettering Cancer Center, New York, NY); Pfeffer, L.; Lipkin, M. *Semin Oncol* 3(4): 369-372; 1976.

Skin fibroblasts (SF) were tested for growth in fetal calf serum (FCS) and for susceptibility to transformation by Kirsten murine sarcoma virus (Ki-MSV). The SF were taken from patients with adenomatosis of the colon and rectum (ACR), from clinically asymptomatic ACR progeny, and from normal controls. SF from normal individuals and from individuals with nonhereditary colon carcinoma grew in a medium containing 5% FCS, but not in 1% FCS. SF from patients with ACR, as well as SF from clinically asymptomatic adults and the progeny of ACR subjects, grew in both 15% and 1% FCS. SF from other children of ACR-afflicted-parents did not grow in 1% FCS. In the second part of the study, transformation of SF by Ki-MSV was attempted with SF from ACR individuals, from clinically asymptomatic ACR progeny, and from normal subjects. The degree to which the various cell types were affected by the virus correlated closely with their serum requirement. Low serum growers were high transformers (100-1,000-fold more susceptible than normal subjects), while low serum nongrowers were low transformers. The virally transformed SF became anchorage-dependent and formed tumors in athymic mice within 8-10 wk. The results suggest the presence of early and previously undetected metabolic lesions in SF from clinically asymptomatic subjects. Experimental results indicate that cell culture morphology, growth in low serum, and susceptibility to transformation by Ki-MSV may be used to identify individuals with latent ACR and a high risk for colon cancer. (35 refs.)

- 77-6653 **Functional Evolution of Cells and Carcinogenesis.** (Rus) Sheveleva, V. S. (Lab. Cellular Physiology, Inst. Cytology, Leningrad, USSR). *Vopr Onkol* 23(6): 96-106; 1977.

Literature on the role of neurohumoral regulation in tumorigenesis is surveyed. Embryonal and early postnatal development is characterized by an anaerobic type of metabolism. Fluorometric measurement of the adrenaline and noradrenaline levels in the sympathetic ganglia showed a significant elevation (by several times) of catecholamine concentration in newborn animals and a progressive increase in acetylcholine with aging. Acetylcholine inhibits the glycolytic effect of catecholamines and blocks the pentose phosphate pathway of glucose oxidation. The function of the sympathetic-adrenal system is disturbed markedly in patients with cancer of the stomach, anacid gastritis, polyposis of the stomach, and peptic ulcer. Patients with tumors of the digestive tract and other sites show destruction of the vegetative and somatic fibers of the myelin membrane, which results in reduced acetylcholine synthesis. The functional characteristics of tumor cells are similar to those of embryonal cells prior to the establishment of cholinergic mechanism. (86 refs.)

- 77-6654 **General Theory of Oncogenesis. I. Theoretical Principles.** (Rus) Mekler, L. B. (Moscow, USSR). *Usp Sovrem Biol* 84(4): 113-127; 1977.

General theories of oncogenesis are presented. On a molecular level, inhibition of the conformational mobility of membrane proteins is the basic (and perhaps only) difference between normal and tumor cells. The malignant transformation of a benign tumor cell involves the appearance on its cell membrane of proteins characteristic of other tissues or organs, resulting in its ability to have partial but specific contacts with cells of other tissues and organs. Malignant cells can also be formed directly by the fusion of two normal cells of different organ or tissue specificity. These cells are able to have specific contacts with two cell types, but the contacts are incomplete and insufficient for contact inhibition. A tumor is regarded as an anomalous, defective, incomplete, and disseminated daughter organism ("embryo"). It is anomalous because it is formed by the fusion of somatic cells, and it is defective because it contains an undifferentiated precursor cell population whose plasma membrane proteins are blocked in a conformation corresponding to the transition from rest to mitosis. In the absence of stimuli of sufficiently high intensity, primary transformed cells can persist for a long time in a dormant state. Endogenous viruses, which are free organ or tissue specific genetic determinants, are formed through destruction of the cell genome; eg, during the fusion of different types of somatic cells that are in different phases of mitosis during fusion. (57 refs.)

- 77-6655 The Implications of Multiple Tumor Induction in Rodent Skin for the Biologic Nature of Neoplasia. (Eng) Shubik, P. (Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, Omaha NB 68105). *Cancer [Suppl]* 40(4): 1821-1824; 1977.

Because of the multiplicity of factors determining induction of tumors by carcinogens, it is suggested that neoplasia is a reactive cellular process with various endpoints. Patterns of tumor progression are outlined, and the independent behavior of multiple tumors is emphasized. (10 refs.)

- 77-6656 Neoplasms of the Skin. (Eng) Meyer, W. (M. D. Anderson Hospital, Houston, TX). *Resident Staff Physician* 23(7): 63-77; 1977.

The proceedings of a clinical conference entitled "Neoplasms of the Skin and Malignant Melanoma" and held at the M. D. Anderson Hospital and Tumor Institute, Houston, Texas, are reported. Discussion is made of the clinical recognition of skin neoplasms, skin tumors in Texas over the past 23 yr, Paget's disease, treatment of precancerous skin lesions and of early and advanced skin carcinomas, and cutaneous angiosarcomas. The NCI and the American Cancer Society estimated that 300,000 new cases of skin cancer would be diagnosed in 1976. Solar radiation probably accounts for most cases of cancer in exposed areas of the skin. (no refs.)

- 77-6657 The Pathogenesis of Bladder Cancer. (Eng) Friedell, G. H. (Dept. Pathology, St. Vincent Hosp., Worcester, MA 01604); Jacobs, J. B.; Nagy, G. K.; Cohen, S. M. *Am J Pathol* 89(2): 431-442; 1977.

Some cases of carcinoma of the urinary bladder appear to arise from carcinoma in situ developing in a field of atypical epithelial proliferation. There is both a spatial and temporal relationship between invasive and in situ bladder cancer, although the exact relationship between the noninvasive flat and papillary types of tumors is not known. Preneoplastic bladder lesions are defined as irreversible, although not necessarily progressive. In Fischer rats, the appearance of pleomorphic microvilli on the luminal surface of epithelial cells of the urinary bladder was correlated with the irreversibility of hyperplastic epithelial lesions induced by ingestion of N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (0.2% for 22 wk). This alteration was visualized by scanning electron microscopy of cytologic and histologic preparations. (21 refs.)

- 77-6658 Newer Insights into the Pathogenesis of Liver Cancer. (Eng) Farber, E. (Dept. Pathology, Banting Inst., 100 College St., Toronto, Ontario, Canada M5G 1L5); Solt, D.; Cameron, R.; Laishes, B.; Ogawa, K.; Medline, A. *Am J Pathol* 89(2): 477-482; 1977.

A model for the pathogenesis of liver cancer is proposed based on the concept that once cells acquire a resistance to the cytotoxicity of a carcinogen, selection factors may favor the replication of these transformed cells over normal cells. The theory is consistent with time of tumor appearance, the inhibitory effect of carcinogens on cell proliferation, and the focal development of tumors; it also helps to explain why host mechanisms might not destroy the tumor cells. (16 refs.)

- 77-6659 Acute Leukemia after Treatment of Lymphoma. (Letter to Editor). (Eng) Rowley, J. D. (Univ. of Chicago, Chicago, IL 60637); Golomb, H. M.; Vardiman, J. W. *N Engl J Med* 297(18): 1013; 1977.

Acute nonlymphocytic leukemia developed in 10 patients after chemotherapeutic treatment for malignant lymphoma. Leukemia developed 29 to 132 mo after diagnosis of lymphoma, and average survival after onset of leukemia was 3.5 mo. In all patients, chromosomal abnormalities with cytopenia were definite indicators of the preleukemic state. (4 refs.)

- 77-6660 Mutation and Cancer in Man. (Eng) Knudson, A. G. (Inst. Cancer Res., 7701 Burholme Ave., Philadelphia, PA 19111). *Cancer [Suppl]* 39(4): 1882-1886; 1977.

Cancer appears to arise in genetically susceptible individuals as a consequence of one germinal (prezygotic) and one somatic mutation. However, two postzygotic (somatic) mutations are apparently involved in normal individuals. Because of geographic variations in cancer incidences, environmentally caused mutations, rather than spontaneous mutations, appear to be a deciding factor in carcinogenesis. Radiation, chemicals, and, perhaps, viruses may increase the incidence of cancer by increasing mutation rates above background levels. People may be classified according to their cancer risk into those genetically predisposed, those exposed environmentally, and those influenced by both or neither. The excess of cancer in industrialized nations is probably due to chemical agents entering the environment from industry and to chemical agents in diet. (12 refs.)

- 77-6661 Familial Susceptibility to Lung Cancer and Chronic Obstructive Pulmonary Disease (Letter to Editor). (Eng) Lynch, H. T. (Dept. Preventive Medicine, Public Health, Creighton Univ. Sch. Medicine, Omaha, NE 68178); Guirgis, H. A.; Harris, R. E. *Lancet* 2(8042): 815; 1977.

An association between lung cancer and chronic obstructive pulmonary disease (COPD) was noted in 12 families prone

to lung cancer. There were 29 verified lung cancer patients in the pedigrees, and there was a significant excess of cancer at all anatomic sites in first-degree relatives, compared with second- and third-degree relatives. Prolonged exposure to an environmental carcinogen may be necessary before the phenotypic expression of lesions such as lung cancer in susceptible individuals. Careful evaluation of associated pulmonary disease in at-risk patients is warranted. (3 refs.)

77-6662 Mucus-producing Cells of the Tracheobronchial Tree. (Eng) Meyrick, B. (Dept. Experimental Pathology, Cardiothoracic Inst., Brompton Hosp., Fulham Road, London, SW3 6HP, England). *Adv Exp Med Biol* 89: 61-76; 1977.

Incorporation of ^3H -threonine and ^3H -glucose by the mucous and serous cells of bronchial gland specimens from lung cancer patients was studied. A significantly greater amount of both radioactive precursors was bound by the mucous cells than the serous cells. In the airway itself, irritants such as tobacco smoke and sulfur dioxide can transform a serous cell or Clara cell into a goblet cell, depending on location. The origin of the mucous and serous cells is discussed. (23 refs.)

77-6663 Histology and Pathogenesis. (Eng) Workshop on Lung Cancer (Geneva, Switzerland). In: *Lung Cancer. A Series of Workshops on the Biology of Human Cancer*. Wynder, E. L.; Hecht, S., eds. (Geneva: International Union Against Cancer): Vol 25(3), pp. 43-64; 1976.

A review of the literature on the premalignant states in lung cancer, general features of the disease, and a classification of different lung tumors is presented. The origin and the histology of the different tumors are discussed. (54 refs.)

77-6664 Some Epidemiological Data on Lung Cancer in the USSR. (Eng) Bogovski, P. (Inst. Experimental and Clinical Medicine, Ministry Health Estonian SSR, 42 Hiiu St., Tallinn 200015, Estonian SSR); Purde, M.; Rahu, M. *IARC Sci Publ* (16): 241-246; 1977.

Epidemiological studies in different parts of the USSR are surveyed. These studies, which cover such diverse areas as the Far East, Northern Caucasus, Ukraine, Byelorussia, Northwestern area of the Estonian SSR, and Moscow, show positive correlations between lung cancer mortality rates and smoking, industrialization, and urbanization. During 1968-1972, the urban:rural standardized morbidity ratio was 1.2:-1.0 for men and 1.1:1.0 for women. The morbidity among urban populations was 8.9 times higher in men than in women; that in rural populations was 10.1 times higher in men than in women. A cartographic analysis of standardized lung

cancer mortality rates in 53 cities and towns and of the location of various industries showed relationships in space and time between lung cancer mortality and atmospheric pollution. (18 refs.)

77-6665 Cancer and Occupation: Status and Needs of Epidemiologic Research. (Eng) Cole, P. (Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA 02115). *Cancer [Suppl]* 39(4): 1788-1791; 1977.

The contributions of epidemiologic research to the identification of occupational cancer hazards and control are reviewed. Existing epidemiologic methods permit identification of groups at high risk of cancer because of their occupational experience. Retrospective follow-up studies have two major disadvantages: the long time lapse between the introduction of a carcinogen into the work environment and its recognition as such and the reliance on mortality rather than incidence data. Factors that should be evaluated in studies of occupational carcinogenesis are the magnitude of the increased cancer risk following exposure to a carcinogen, the relationship of excess risk to age at start of exposure, the effect of duration of exposure, the duration of the interval between beginning exposure and manifestation of the disease, and the ways in which occupational exposures may modify the effects of other carcinogens. Existing epidemiologic methods can demonstrate occupational carcinogenesis even when the excess risk is rather small and the disease is relatively common in the general population. It is suggested that an exposure-specific occupational code be developed by a national or international body. Epidemiologic approaches to mortality reduction can be in the form of improving the design and evaluation of early disease-detection programs. (16 refs.)

77-6666 Riboflavin. (Eng) Foy, H. (Wellcome Trust Res. Labs., Post Office Box 14336, Nairobi, Kenya); Mbaya, V. *Prog Food Nutr Sci* 2(8): 357-394; 1977.

The role of riboflavin (RF) in the human diet and its metabolism are reviewed. In the baboon, complete RF deficiency for 160-240 days induced esophageal lesions resembling human preneoplastic lesions. Because RF is an essential factor in maintaining the squamous epithelium of the esophagus, RF deficiency may increase the susceptibility of this tissue to environmental carcinogens and subsequently potentiate esophageal malignancy. The link of RF with adrenal functions should also be considered when examining its role in carcinogenesis. Tumors that regress with RF deficiency are probably associated with immunological factors, whereas RF's inhibitory effects on various hepatic chemical carcinogens may be associated with its role in detoxifying reactions. In any case, RF operating at the cellular level may affect the outcome of the effects of carcinogens or of spontaneous tumors. (341 refs.)

CHEMICAL CARCINOGENESIS

- 77-6667 **Aflatoxin B₁, a Selective Inhibitor of DNA Synthesis in Mammalian Cells.** (Eng) Meneghini, R. (Dept. Biochemistry, Inst. Chemistry, Univ. Sao Paulo, C. P. 20780, Sao Paulo, Brazil); Schumacher, R. I. *Chem Biol Interact* 18(3): 267-276; 1977.

The effect of aflatoxin B₁ (AFB₁) on DNA synthesis was investigated in African green monkey kidney cells. Addition of 0.1 µg/ml AFB₁ to the cells inhibited DNA synthesis, but not immediately: synthesis decreased slowly and reached 32% after 3 hr, after which it leveled off. This concentration had little effect on protein or RNA synthesis. Addition of 0.001-1 µg/ml AFB₁ had little effect on repair of UV light-induced DNA damage, but DNA synthesis was inhibited. This inhibition was irreversible up to 8 hr after removal of AFB₁; the inhibition was at the initiation stage. Thus, chain growth in AFB₁-treated cells was the same as that in control cells. The reason why elongation is not affected is not clear. (23 refs.)

- 77-6668 **Effect of Aflatoxin B₁ on Hepatic Polyribosomes and Protein Synthesis in the Rat.** (Eng.) Sidransky, H. (Dept. Pathology, George Washington Univ. Medical Center, 2300 Eye St., N.W., Washington, DC 20037); Verney, E.; Murty, C. N.; Sarma, D. S.; Reid, M. *Chem Biol Interact* 18(1): 69-82; 1977.

The effect of aflatoxin B₁ (AFB: 6.0 mg/kg ip) on hepatic polyribosomes (free and membrane-bound), protein synthesis, and activity of initiation factors in rats within 3, 6, and 12 hr after treatment was investigated. AFB led to a progressive disaggregation of free and membrane-bound polyribosomes, inhibition of in vitro protein synthesis by both populations of polyribosomes, and to defective ribosomes, particularly the 60S ribosomal subunits, of both types of polyribosomes. AFB had little or no effect on the activities of initiation factors. In comparative studies with actinomycin D (A-D), AFB decreased RNA synthesis by 73%, decreased in vitro protein synthesis by 58%, and prevented the induction of hepatic tryptophan pyrrolase by cortisone, but A-D decreased RNA synthesis by 80%, in vitro protein synthesis by 54%, and prevented the induction of tryptophan pyrrolase. However, there was progressive disaggregation of only the free polyribosomes after A-D. (40 refs.)

- 77-6669 **Distribution of Aflatoxin B₁ in Tissues of Mink (*Mustela vison*).** (Eng) Chou, C. C. (Dept. Food

Science, Univ. Wisconsin-Madison, Madison, WI 53706; Marth, E. H. *Toxicology* 5(3): 351-358; 1977.

Seven female mink (*Mustela vison*, 470-650 g) were inoculated ip with ¹⁴C-labeled and unlabeled aflatoxin B₁ at a total dose of 100 µg/kg and 2.3-3.1 x 10⁶ disintegrations/min ¹⁴C. After sacrifice at 1, 2, 4, and 24 hr after toxin administration, the distribution of ¹⁴C radioactivity in the liver, intestine, stomach, bile, lung, heart, kidney, brain, pancreas, spleen, urinary bladder, and uterus was measured. At 1 hr after administration, the intestines and their contents contained the largest amount (18.9%), followed by the liver (13.2%) and bile (10.8%). In general, radioactivity steadily decreased in the tissues with time. However, at 4 and 24 hr after injection the radioactivity of liver tissue (8.8% and 6.6%, respectively) exceeded values obtained for the other organs. Data on the distribution of radioactivity among the particular fractions of the liver showed that the microsomal supernatant fluid retained most of the radioactivity over the 24-hr period. Thus, the retention of aflatoxin and/or its metabolites in the mink liver may account for the prominent liver damage caused in this animal. (10 refs.)

- 77-6670 **Bovine Liver Metabolism and Tissue Distribution of Aflatoxin B₁.** (Eng) Hayes, J. R. (Div. Nutritional Sciences, Cornell Univ., Ithaca, NY 14853); Polan, C. E.; Campbell, T. C. *J Agric Food Chem* 25(5): 1189-1193; 1977.

Studies were performed to determine types of aflatoxin (AF) metabolites produced by bovine liver and which metabolites are found in tissues following in vivo administration. In vitro incubation of 5 µl AFB₁ with bovine liver preparations indicated that about 15% to 22% of the AFB₁ was metabolized to AFQ₁, AFM₁, and two unknowns. Approx 63% of the original AFB₁ material was metabolized to water-soluble products. No AFB₂a, AFP₁ or aflatoxicol were found. In experiments in which cows were fed either 10, 50, 250 or 1250 ppb AFB₁, only the animal fed 1250 ppb AFB₁ had chloroform-soluble metabolites in the edible portion of the carcass. AFB₁ and AFM₁ were the only metabolites found in the brain, heart and muscle. However, muscle and liver contained approx 1.7 ppb and 0.3 ppb of AFB₁ equivalents. It was concluded that chloroform-soluble metabolites present no health hazard to humans consuming edible beef products from animals fed < 4 ppb AFB₁ and negligible carcinogenic hazard from animals fed ≥ 46 ppb. More studies on the hazard due to

water-soluble AF metabolites in meat products must be performed. (41 refs.)

77-6671 Comparative Study of the Fluorescent Characteristics of Solutions of Aflatoxins and Palmoxins in Chloroform. (Eng.) Uwaifo, A. O. (Dept. Biochemistry, Univ. Ibadan, Ibadan, Nigeria); Emerole, G. O.; Bassir, O. *J Agric Food Chem* 25(5): 1218-1220; 1977.

Fluorescent characteristics of aflatoxins B₁, B₂, G₁, and B₃ and palmoxins B₀ and G₀ were similar. Their fluorescence emission maxima fell within the wavelength range of 410-430 nanometers (nm), and they were all excited at 365 nm. Fluorescence intensity was as follows: G₂ > G₁ > G₀ > B₃ > B₀ > B₂ > B₁. (15 refs.)

77-6672 Effect of Aflatoxin B₁, Ochratoxin A and Rubratoxin B on Infant Rats. (Eng.) Hayes, A. W. (Dept. Pharmacology and Toxicology, Univ. Mississippi Medical Center, Jackson, MS 39216); Cain, J. A.; Moore, B. G. *Food Cosmet Toxicol* 15(1): 23-27; 1977.

The 7-day oral LD₅₀ values for aflatoxin B₁, ochratoxin A, and rubratoxin B were 1.36, 3.90, and 6.38 mg/kg, respectively, in 24-hr-old Sprague-Dawley rats. Compared with adults, these neonates demonstrated an increased susceptibility to each mycotoxin tested. When neonates simultaneously received different doses of ochratoxin and constant doses of 1 or 5 mg/kg rubratoxin, the LD₅₀ value was reduced from 3.9 to 2.5 and 0.24 mg/kg, respectively. Various doses of rubratoxin given with 2 mg/kg ochratoxin decreased the rubratoxin LD₅₀ 4.5-fold. In animals given 5 mg/kg rubratoxin at 24 hr followed by 4 mg/kg aflatoxin on day 15, av daily wt gains were reduced as a result of mediation by both agents. When aflatoxin was followed on day 15 by rubratoxin or when ochratoxin was followed by rubratoxin, no synergistic response was demonstrated. Interactive and/or delayed exposure of a young animal could enhance the susceptibility of the adult to other environmental toxicants and/or carcinogens. (24 refs.)

77-6673 Streptozotocin-induced Liver Tumors. (Eng.) Feldman, S. (Dept. Surgery, Washington Univ. Sch. Medicine, Wohl Hosp., St. Louis, MO 63110); Scharp, D.; Hirshberg, G.; Dodi, G.; Ballinger, W.; Lacy, P. *Transplantation* 24(2): 152-154; 1977.

A possible connection had been suggested between long-term transplantation of isolated pancreatic islets via the portal vein and the development of hepatic cysts in streptozotocin (SZ)-induced diabetes. Lewis rats inoculated with SZ (65 mg/kg iv) developed well-established diabetes in ≤ 2 wk, but no pathological liver changes were noted in the nine rats sacrificed within the first 16 wk. However, livers from 15/16 rats

studied from 17 to 72 wk showed severe hepatic damage. Cystic structures lined with a cuboidal epithelium and, occasionally, with mitotic figures, features characteristic of cholangiomas, were present. Livers from 8/9 rats at 17-28 wk revealed single, scattered, and multiple adenomas. All livers (7/7) taken at 29-72 wk showed pathological changes: multiple adenomas, multiple hepatomas, multiple large cystic adenomas, and massive cystic replacement of the liver parenchyma. Rats that received islet isografts via the portal vein after SZ treatment showed identical hepatic lesions. These results indicate that the cholangiomas and hepatomas are induced by the SZ alone. (5 refs.)

77-6674 A Protease Inhibitor Blocks SOS Functions in *Escherichia coli*: Antipain Prevents λ Repressor Inactivation, Ultraviolet Mutagenesis, and Filamentous Growth. (Eng.) Meyn, M. S. (Dept. Pathology, New York Univ. Medical Center, New York, NY 10016); Rossman, T.; Troll, W. *Proc Natl Acad Sci USA* 74(3): 1152-1156; 1977.

Various strains of *Escherichia coli* were incubated with and without antipain [(1-carboxy-2-phenylethyl)carbamoyl-L-arginyl-L-valylargininal], a low-mol-wt protease inhibitor isolated from actinomycetes. In bacteria possessing both *recA* and *lexA* genes, the frequency of UV-induced Trp⁺ revertants/10⁷ bacteria was reduced 70%-90%, indicating a drastic reduction in mutagenesis. At 0.5 mM, antipain did not inhibit total RNA or protein synthesis, cell growth, or induction of β-galactosidase, but appeared to specifically block error-prone DNA repair (SOS repair). Antipain also blocked expression of thermally induced mutator activity in a *tif-1* mutant, WP44s-NF, that expresses coordinately controlled SOS functions (including λ prophage induction, filamentous growth and SOS repair) at 42 C without inhibition of DNA synthesis or detectable DNA damage. The results support the hypothesis that λ repressor is normally inactivated by an irreversible proteolytic action and provide evidence suggesting that proteases play a key role in the induction of SOS functions. (46 refs.)

77-6675 A New Endonuclease from *Escherichia coli* Acting at Apurinic Sites in DNA. (Eng.) Ljungquist, S. (Dept. Chemistry, Karolinska Inst., 104 01 Stockholm, Sweden). *J Biol Chem* 252(9): 2808-2814; 1977.

A new DNA endonuclease, endonuclease IV, was isolated from *Escherichia coli* B/r and characterized. The enzyme has a broad pH optimum of 8.0 to 8.5; it is unaffected by EDTA, unusually resistant to NaCl, relatively heat-stable, and not inhibited by *E. coli* or yeast transfer RNA. Physical data indicate that it is an asymmetric globular protein with a mol wt of 33,000. No exonuclease or 3'-phosphatase activity was associated with the enzyme. The enzyme specifically catalyzes the formation of single-strand breaks at apurinic and apyrimidinic sites in DNA, but has no activity on intact or single-stranded DNA. The enzyme shows little or no activity

on UV-irradiated DNA unless the DNA is further heated before treatment. It does show activity on x-irradiated DNA, probably on apurinic and apyrimidinic sites introduced by the radiation treatment. This enzyme is one of several endonucleases that can incise double-stranded DNA at apurinic sites. Since there are multiple modes of repair of this type of DNA damage, an apurinic site is rarely expressed as a mutagenic event. (42 refs.)

- 77-6676 **Effect of Dietary Polyunsaturated Fat on the Growth of a Transplantable Adenocarcinoma in C3HavvB Mice.** (Eng) Hopkins, G. J. (Dept. Biochemistry, Health Sciences Centre, Univ. Western Ontario, London, Ontario N6A 5C1, Canada); West, C. E. *J Natl Cancer Inst* 58(3): 753-756; 1977.

Weanling male and female C3HavvB mice were fed a low-fat (4.5%) diet until age 60-70 days, when they were fed high-fat (18.6%) diets containing sunflower-seed oil (polyunsaturated fat diet) or tallow (saturated fat diet). After 4 wk on the high-fat diets, each mouse received an inoculum of approx 1,700 single cells from a transplantable mammary adenocarcinoma. The cumulative incidence of tumor-bearing mice was significantly greater among males and females fed the polyunsaturated fat diet than among those fed the saturated fat diet. The mean times elapsed before palpable tumors developed were less when mice were fed the polyunsaturated fat diet than when mice were fed the saturated fat diet, but these differences were not statistically significant. The cumulative incidence of tumor-bearing mice was also significantly greater among females than males. The results support previous suggestions that a polyunsaturated fat diet exerts its effect on the promotional stage of carcinogenesis rather than on the initial event of neoplastic transformation. (25 refs.)

- 77-6677 **Spectral and Metabolic Characteristics of Mitochondrial Fractions from Rotenone-induced Tumours.** (Eng.) Gosalvez, M. (Bioquímica Experimental, Clinica Puerto de Hierro, Facultad de Medicina, Universidad Autonoma, Madrid, Spain); Diaz-Gil, J.; Coloma, J.; Salganicoff, L. *Br J Cancer* 36(2): 243-253; 1977.

Mitochondrial fractions isolated from transplanted and primary tumors induced by rotenone (1.7 µg/g x 40-50 days, ip) in Wistar rats were investigated. The rotenone-induced tumors lack respiratory control and oxidative phosphorylation from the initial growth, and this fact must correspond to the structural alterations of the mitochondria in situ. The mitochondria of these tumor cells are characterized by partial or total insensitivity to cyanide or other respiratory inhibitors, a low content in flavoprotein and, perhaps, in cytochrome a, and the lack of respiratory control and oxidative phosphorylation. This suggests that the structural and biochemical alterations of rotenone-induced tumors may be due to a lack of mitochondrial differentiation when the tumors

develop from the atrophic mammary gland. It is also suggested that these tumors depend on glycolysis for their sole source of energy. (30 refs.)

- 77-6678 **Differential Effects of Phenobarbital and 3-Methylcholanthrene on Rat Hepatic Ribosomal Precursor RNA.** (Eng) Smith, S. J. (Dept. Pharmacology, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA 17033); Leonard, T. B.; Ducean, B. W.; Vesell, E. S. *Biochem Pharmacol* 26(10): 955-961; 1977.

Synthesis of hepatic ribosomal precursor RNA (45S rRNA) was investigated in male Sprague-Dawley rats treated with single ip injections of methylcholanthrene (MC; 30 mg/kg) or phenobarbital (PB; 100 mg/kg). In vivo labeling of total nuclear RNA and of nuclear 45S rRNA with ³H-orotic acid was unchanged in rats sacrificed 3 or 20 hr after MC injection. These results agree with in vitro measurements of nucleolar RNA polymerase activity, which was unaffected by either MC or PB. In rats sacrificed 6 hr after receiving PB or 3 or 20 hr after receiving MC, incorporation of ³H-uridine triphosphate into isolated nucleoli was not enhanced. In vivo labeling of microsomal 28S and 18S rRNA with (³H)-orotic acid increased 50% 6 hr after PB injection, but was unchanged 3 or 20 hr after MC. The stability of 45S rRNA in rats treated with PB or MC was tested in a nuclear incubation system. Sucrose gradient analysis of extracted RNA indicated that 16 hr after PB treatment, the stability of 45S rRNA was increased over that of controls, whereas 20 hr after MC 45S rRNA stability was unchanged. These results suggest that PB, but not MC, enhances the posttranscriptional stability of 45S rRNA and in vivo labeling of microsomal RNA. Neither MC nor PB increases the synthesis of ribosomal precursor RNA. (56 refs.)

- 77-6679 **Effect of Ascorbic Acid on Tumour Growth.** (Eng) Migliozi, J. A. (Dept. Pathology, Peoria Sch. Medicine, Univ. Illinois, Peoria, IL 61606). *Br J Cancer* 35(4): 448-453; 1977.

To determine whether vitamin C is a necessary requirement for tumor growth, 85 strain 2 guinea pigs were given a single injection of 20-methylcholanthrene (40 mg sc), and the 6 that developed tumors were divided into three groups and treated po with the vitamin. Group 1 received 10 mg ascorbic acid/kg/day (controls), group 2 0.3 mg/kg/day and supplements from time to time to prevent death, and Group 3 received 1 g/kg/day. After 168 days, the doses were reversed. Group 3 was given 0.3 mg and Groups 1 and 2 were given 1 g/kg. Increased tumor growth was noted in Group 3 guinea pigs, and the typical histology of their tumors is described. By 20 wk, 11/20 animals had died. Of 20 Group 2 animals, 16 showed inhibition of tumor growth between 4 and 8 wk and 11 tumors regressed completely by 20 wk. Of the Group 1 animals, growth inhibition was noted in 10 by 20 wk, but

had normal tumor growth. Of the Group 3 guinea pigs fed 0.3 mg/kg after 20 wk, all died within 3 wk with signs of scurvy. Two Group 2 animals and three Group 1 animals had enhanced tumor growth when 1 g/kg was administered. Although these tumors had been inhibited, they did not regress by the time the diet was changed. In Group 3 guinea pigs, ascorbic acid levels in the tumor and WBC increased when the vitamin level was increased to 1 g; in Group 2 animals, the level in the WBC fell when the diet was changed, but the tumor level remained high. The results indicate that ascorbic acid is necessary for tumor growth in this system. (14 refs.)

77-6680 **Authoradiographic Study of DNA Metabolism in Different Lymphocyte Populations in BALB/c Mice During Chemical Carcinogenesis.** (Rus) Umansky, Iu. (Dept. Carcinogenesis Immunity, Inst. Problems Oncology, Acad. Sciences Ukrainian SSR, Kiev, USSR); Gudimov, K. A. *Tsitologiya* 19(9): 1000-1005; 1977.

Changes in DNA metabolism were studied in different lymphocyte populations of male BALB/c mice during the development of a sarcoma induced by methylcholanthrene (1 mg injected into the right hind limb). The animals were sacrificed during the first 4.5 mo, 1 hr after the administration of ³H-thymidine for autoradiographic studies. In the regional lymph nodes, the percentage of macronuclear lymphocytes increased from 67.1% to 41.6% at 4-4.5 mo, and their labeling index rose from 1.54% to 5.29%. The percentage of micronuclear lymphocytes increased accordingly from 25.9% to 49.4%, but their labeling index remained practically unchanged (1.68% vs 1.57% after 4-4.5 mo). The percentage of lymphoblasts increased from 4.7% to 6.7%, their labeling index from 45.39% to 57.90%. Changes in the ratio of macronuclear and micronuclear lymphocytes, lymphoblast counts, and the cell labeling indices were less marked in distant lymph nodes. (15 refs.)

77-6681 **Preliminary Studies on Mutagenicity of Saccharin by Induction of Dominant Lethals.** (Eng) Mezbawala, B. U. (ICMR Unit for Studies on Environmental Carcinogens, Cancer Res. Inst., Parel, Bombay-400 012, India); Gothoskar, S. V. *Indian J Cancer* 14(3): 232-234; 1977.

Male C17 and Swiss mice were injected sc with 100, 240, or 480 mg/kg saccharin and then mated with females of the same strain. A significant number of dominant lethal mutations, defined as the ratio of dead embryos to the total number of embryos, were noted during the second and third wk of pregnancy. In C17 mice whose mates had been treated with 240 or 480 mg/kg. In Swiss mice, the effect was only significant during the third wk of pregnancy in mice whose mates had received 240 mg/kg. (13 refs.)

77-6682 **The Mutagenicity of Saccharin Impurities. I. Detection of Mutagenic Activity.** (Eng) Stoltz, D. R. (Toxicology Res. Div., Health Protection Branch, Tunney's Pasture, Ottawa, Canada K1A 0L2); Stavric, B.; Klassen, R.; Bendall, R. D.; Craig, J. *J Environ Pathol Toxicol* 1(1): 139-146; 1977.

Sodium saccharin, o-toluenesulfonamide, and impurities extracted from commercial saccharin by water and organic solvents were tested for mutagenicity with *Salmonella typhimurium*. The organic solvent-soluble impurities exhibited strong mutagenic activity for TA98 and slight activity for TA100. Mutagenic activity for *S. typhimurium* TA98 was demonstrated in extracts of some but not all sodium saccharin samples produced by both the Maumee and Remsen-Fahlberg processes. The relevance of the mutagenic impurity to the carcinogenicity of saccharin is discussed. (11 refs.)

77-6683 **Inhibition of Carcinogenic Effects of Polycyclic Hydrocarbons by Benzyl Isothiocyanate and Related Compounds.** (Eng) Wattenberg, L. W. (Dept. Lab. Medicine and Pathology, Univ. Minnesota Medical Sch., Box 609, Mayo Memorial Building, Minneapolis, MN 55455). *J Natl Cancer Inst* 58(2): 395-398; 1977.

The inhibition of carcinogenesis by benzyl isothiocyanate, benzyl thiocyanate, and phenethyl isothiocyanate, compounds found in cruciferous plants, and by phenyl isothiocyanate, a synthetic compound, was studied in two test systems. In the first, the four compounds (23-50 mg, po) were given 2, 4, or 24 hr before or 4 hr after administration of 7,12-dimethylbenz(a)anthracene (DMBA: 12 mg, po) to female Sprague-Dawley rats. Mammary tumor formation was inhibited only when the agents were given 4 hr prior to DMBA. Benzyl isothiocyanate was more potent than benzyl thiocyanate or phenethyl isothiocyanate. At the dose level used (23 mg) phenyl isothiocyanate appeared to be slightly more potent than benzyl isothiocyanate (50 mg). In the second system, the four compounds were tested on formation of tumors of the forestomach and lungs in female ICR/Ha mice fed diets containing the inhibitor plus benzo(a)pyrene (BP: 0.3 mg/g diet) or DMBA (0.05 mg/g diet). Addition of benzyl isothiocyanate (5.0 mg/g diet) or phenethyl isothiocyanate (5.5 mg/g diet) profoundly inhibited both BP- and DMBA-induced neoplasms of the forestomach. Benzyl thiocyanate (5.0 mg/g diet), however, showed no inhibition. The number of pulmonary adenomas per animal was also reduced significantly by benzyl isothiocyanate and phenethyl isothiocyanate. These compounds occur in foods that are eaten by man, and they may act to diminish the effect of chemical carcinogens. (20 refs.)

77-6684 **Carcinogenic & Alkylating Potencies of Various Bromomethylated Compounds (Meeting Abstract).** (Eng) Croisy, A. (Institut du Radium, INSERM, U

22, Faculte des Sciences, 91405-Orsay, France); Zajdela, F.; Croisy-Delcey, M.; Jacquignon, P. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 83; 1977. (no refs.)

77-6685 Autoradiographic and Histopathologic Studies on the Mode of Action of an Aromatic Retinoid (Ro 10-9359) on Chemically Induced Epithelial Tumors in Swiss Mice. (Eng) Frigg, M. (Dept. Vitamin and Nutritional Res., F. Hoffmann-La Roche & Co., Ltd., Basel, Switzerland); Torhorst, J. *J Natl Cancer Inst* 58(5): 1365-1371; 1977.

The mode of action of an aromatic analog of retinoic acid, ethyl all-trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoate (Ro 10-9359), was investigated by autoradiographic and histopathologic methods. In female Swiss mice with 7,12-dimethylbenz(a)anthracene-induced skin papillomas, a single ip injection of 1,000 mg/kg Ro 10-9359 caused a 29% regression in mean tumor diameter after 3 days and a 51% regression after 7 days. The number of tumor cells synthesizing DNA and the length of the cell cycle were not affected by the retinoid. These findings exclude any mode of action at the level of cell proliferation. The retinoid accelerated cell loss in the upper epidermal layers, but this effect was not sufficient to explain the tumor regression. Quantitative histometry indicated that a reduction in the area of the horn and the formation of large necroses were mainly responsible for the tumor regression in the Ro 10-9359-treated group. After 7 days, the proportion of stroma in the tumors increased, and there were frequent dilations of the stromal vessels and edema in the proximity of the necroses. (22 refs.)

77-6686 Stages in Neoplastic Transformation of Adult Epithelial Cells by 7,12-Dimethylbenz(a)anthracene In Vitro. (Eng) Knowles, M. A. (Dept. Cellular Pathology, Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Franks, L. M. *Cancer Res* 37(11): 3917-3924; 1977.

Explant cultures of submandibular glands from adult C57BL mice were used to establish five tumor-producing cell lines. Four lines were from cultures treated for 24 hr on day 4 of culture with 7,12-dimethylbenz(a)anthracene. Three of these gave rise to adenocarcinomas after transplantation into syngeneic mice; the fourth produced tumors with carcinomatous and sarcomatous areas. The fifth cell line was derived from an untreated culture, and it gave rise to adenocarcinomas. A series of four well-defined morphological stages occurred in the cultures before tumor-producing cell lines were established. In Stage I (0-30 days), there was an outgrowth of epithelium; in Stage II (30-70 days) ductal differentiation occurred in some epithelium; in Stage III (70-100 days), small, slowly proliferating foci developed either from the ducts or

from flat epithelial areas. In Stage IV (> 100 days), the proliferation rate in some foci increased, and the cells became more irregular. The cells could not be transferred easily until about 150 days, after which they were tumor-producing. Neoplastic transformation occurred between 158 and 240 days in the treated cultures and at 325 days in the untreated culture. (21 refs.)

77-6687 The Effect of Dimethylbenzanthracene and Benzo(a)anthracene on the Biogenic Amine Level in Rat Brain. (Rus.) Anisimov, V. N. (Inst. Experimental Medicine, USSR Acad. Medical Sciences, Leningrad, USSR); Pozdeev, V. K.; Dmitrievskaia, A. Iu.; Gracheva, G. M.; Il'in, A. P.; Dil'man, V. M. *Vopr Onkol* 23(7): 34-38; 1977.

The effects of dimethylbenzanthracene (DMBA) and benzo(a)anthracene on the level of biogenic amines in rat brain were investigated. Thirty min after 5 mg of DMBA iv, norepinephrine, dopamine, serotonin (5-HT) and 5-hydroxyindolacetic acid (HIAA) was decreased in the hypothalamus; monoamine levels in the brain stem and hemispheres were unchanged. Following 5 mg iv benzo(a)anthracene, the level of 5-HT in the hypothalamus was decreased, whereas catecholamine and HIAA levels were unchanged. Levo-dihydroxyphenylalanine (L-DOPA) and alpha-methyl-DOPA pretreatment respectively abolished and increased the 20-methylcholesterol-induced elevation of the threshold of hypothalamic sensitivity to estrogen suppression. It is suggested that hypothalamic mechanisms are involved in the carcinogenic action of polycyclic hydrocarbons in rats. (2 refs.)

77-6688 Effects of Depot Injections of Retinyl Palmitate on 7,12-Dimethylbenz(a)anthracene-Induced Preneoplastic Changes in Rat Skin. (Eng) Brown, I. V. (Dept. Pathology, Health Sciences Center, State Univ. New York, Stony Brook, NY 11794); Lane, B. P.; Pearson, J. *Natl Cancer Inst* 58(5): 1347-1355; 1977.

The preneoplastic changes induced by topical application of 7,12-dimethylbenz(a)anthracene (DMBA: 1 mg 3 times/week) to adult Sprague-Dawley rat skin did not appear when the animals were pretreated locally with depot im injections of retinyl palmitate (RP: 50,000 IU). The epidermal histology after RP-DMBA treatment was similar to that seen in animals exposed to RP alone. RP produced epithelial hyperplasia, inhibition of keratinization, parakeratosis, intercellular edema, and loss of hair overlying the injection site. There was no cellular atypia, irritation, or mucous metaplasia. Ultrastructurally, RP induced a marked decrease in tonofibrils and an increase in epidermal chromatin. DMBA alone induced marked hyperplasia, hyperkeratosis, and cellular atypia of prickle and basal cells that progressed to giant tumor cells. Loss of desmosomes, increased tonofibrils

and defects in the basement membrane were also seen. The preneoplastic changes induced by DMBA did not regress when treatment was discontinued at 6 wk; treatment for > 6 wk exacerbated the abnormal state. In P-DMBA animals, no preneoplastic changes were observed at 6 wk. The mode of interaction between RP and DMBA remains to be defined. (55 refs.)

-6689 Inhibition of the Tumor-initiating Ability of the Potent Carcinogen 7,12-Dimethylbenz(a)anthracene by the Weak Tumor Initiator 1,2,3,4-benzanthracene. (Eng.) Slaga, T. J. (Cancer and Toxicology Program, Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Boutwell, R. K. *Cancer Res* (1): 128-133; 1977.

200 nanomoles (nmol), the weak tumor initiator 1,2,3,4-benzanthracene (DBA) increased the epidermal aryl hydrocarbon hydroxylase (AHH) activity of Charles River CD-1 mice > 10 times that of acetone controls at 12 hr posttreatment. Topical application of the same quantity of the potent initiator 7,12-dimethylbenz(a)anthracene (DMBA) increased AHH activity fourfold over that of controls at 12 hr. Simultaneous treatment with 200 or 100 nmol of DMBA and DBA resulted in AHH activity that was 546% and 732% that of controls, respectively; this activity was lower than that induced by DBA alone. When given at the same time as DMBA, DBA effectively inhibited skin tumor initiation by DMBA. The results suggest that DBA may program the epidermal AHH system to metabolize DMBA to noncarcinogenic metabolites. (44 refs.)

-6690 Inverse Correlation Between Species Life Span and Capacity of Cultured Fibroblasts to Bind 7,12-Dimethylbenz(a)anthracene to DNA. (Eng.) Schwartz, G. (Fels Res. Inst., Temple Univ. Medical Sch., Philadelphia, PA 19140); Moore, C. J. *Exp Cell Res* 109(2): 448-50; 1977.

Three independent fibroblast strains (skin and lung) were isolated from rats, guinea pigs, rabbits, cows, elephants, and man; and the ability of labeled 7,12-dimethylbenz(a)anthracene to bind to the DNA of these cells was examined. An inverse relationship between species life span and rate of carcinogen binding was observed, suggesting that shorter-lived species are more susceptible to environmental carcinogens than longer-lived species. (12 refs.)

-6691 Effects of a Gonadotropin-releasing Hormone (GnRH) Analogue (A-43818) on 7,12-Dimethylbenz(a)anthracene-induced Rat Mammary Tumors. Histological and Endocrine Studies. (Eng.) Danguy, A. (Laboratoire d'Histologie, Faculte de Medecine, 97 rue

aux Laines, 1000 Brussels, Belgium); Legros, N.; Heuson-Stiennon, J.; Pasteels, J. L.; Atassi, G.; Heuson, J. C. *Eur J Cancer* 13(10): 1089-1094; 1977.

The effect of A-43818 [D-leu⁶(des-gly-NH¹⁰₂, proethylamide⁹)] gonadotropin-releasing hormone (GnRH) was investigated in Sprague-Dawley rats bearing 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors. Tumor growth was significantly inhibited by the administration of 10 µg A-43818, twice daily for 6 wk. A dose of 25 µg seemed less effective. Controls and experimental groups were subjected to radioimmunoassays of serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin (PRL) and to histological examination of pituitaries and ovaries. Treatment with A-43818 resulted in atrophy of the pituitary lactotropes and decreased PRL concentration in the plasma. Plasma LH levels were enhanced, but FSH levels remained unchanged. The endocrine mechanisms of inhibition of tumor growth are discussed in light of the well-known hormone dependence of DMBA-induced mammary tumors. (24 refs.)

77-6692 Regulation of Hormone Receptor Levels and Growth of DMBA-induced Mammary Tumors by RU16117 and Other Steroids in the Rat. (Eng.) Kelly, P. A. (Med. Res. Council Group in Molecular Endocrinology, Le Centre Hospitalier de l'Universite Laval, Quebec G1V 4G2, Canada); Asselin, J.; Labrie, F.; Raynaud, J. P. *Prog Cancer Res Ther* 4: 85-101; 1977.

A study was made of the effect of 11α-methoxyethyl estradiol (RU16117), which has potent antiestrogenic properties, on the development and growth of dimethylbenzanthracene (DMBA)-induced mammary tumors in rats. To correlate tumor response to antiestrogen treatment with hormone receptor levels, the concentration of receptors for estradiol-17β, progesterone (PRG) and prolactin (PRL) was determined in individual tumors. Specific binding of ³H-estradiol, the synthetic progestin ³H-R5050, and ¹²⁵I-PRL was performed. RU16117, administered the day after DMBA injection at the relatively low doses of 8 and 24 µg/day, inhibited tumor development completely in all animals. Ovariectomy also inhibited tumor appearance until day 95, when 2/14 rats developed palpable tumors. Studies were also made to determine the effect of RU16117 on the growth of established DMBA tumors. Although a 4-wk treatment with 2 µg/day of RU16117 had little effect on the growth of established tumors, 8 and 24 µg/day led to 45% and 65% inhibition of tumor number, respectively. Ovariectomy had an effect similar to that of 24 µg/day RU16117, which also led to a marked reduction of total tumor size. Combined treatment with estradiol plus PRG or PRL enhanced tumor growth. The levels of receptors for estrogen, PRG, and PRL were increased to control values by these treatments, suggesting a correlation between the effect of hormones on the level of hormone receptors and tumor growth. The data show that estrogenic control of the PRG receptor exists in the DMBA mammary tumor.

However, the PRL receptor is probably also implicated in the control of the PRG receptor, since the estrogen receptor seems to depend on PRL. (37 refs.)

- 77-6693 **Authoradiographic Localization of Prolactin Receptors in 7,12-Dimethylbenz(a)anthracene-induced Rat Mammary Carcinoma.** (Eng.) Costlow, M. E. (Dept. Biochemistry, St. Jude Children's Res. Hosp., 332 N. Lauderdale, Memphis, TN 38101) McGuire, W. L. *J Natl Cancer Inst* 58(4): 1173-1175; 1977.

Prolactin receptors were localized by autoradiography in 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors of Sprague Dawley rats by incubation of tumor slices with ^{125}I -ovine prolactin. Specific prolactin binding was confined to the tumor cells; non-specific binding was present in the alveolar spaces and connective tissue. In some tumors, all cells contained receptors; in others, up to one-half the cells remained unlabeled. These results suggest that variation in receptor content in DMBA-induced mammary tumors may be caused by two distinct cell populations—one containing receptors and another possessing few or no receptor sites. (12 refs.)

- 77-6694 **Predominant Role of Prolactin in Stimulating the Growth of 7,12-Dimethylbenz(a)anthracene-induced Rat Mammary Tumor.** (Eng.) Manni, A. (Dept. Medicine, Case Western Reserve Univ., Cleveland, OH 44106); Trujillo, J. E.; Pearson, O. H. *Cancer Res* 37(4): 1216-1219; 1977.

The role of prolactin in supporting the growth of 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors was studied in Sprague-Dawley rats with estrogen receptors blocked by tamoxifen. Tamoxifen (200 $\mu\text{g}/\text{day}$, sc) did not impair the growth of tumors induced by perphenazine-stimulated prolactin at any time, even when treatment was prolonged up to 50 days. After tumor regression induced by oophorectomy and/or tamoxifen, perphenazine restored tumor growth. In intact tumor-bearing rats, the tumor regression induced by tamoxifen and the prolactin inhibitor lergotril mesylate was reversed by perphenazine. Estrogen receptors measured at the time of max perphenazine stimulation were undetectable. On the other hand, estradiol did not stimulate tumor growth when serum prolactin levels were depressed by lergotril. These results indicate that estrogen receptors are not involved in the prolactin stimulation of DMBA-induced rat mammary tumors. (13 refs.)

- 77-6695 **High Inhibitory Activity of a New Antiestrogen, RU 16117 (11 α -Methoxy Ethinyl Estradiol), on the Development of Dimethylbenz(a)anthracene-induced Mammary Tumors.** (Eng.) Kelley, P. A. (Medical Res. Council Group in Molecular Endocrinology, Le Centre Hospitalier

de l'Universite Laval, Quebec GV 4G2, Canada); Asselin, J.; Caron, M. G.; Raynaud, J. P.; Labrie, F. *Cancer Res* 37(1): 76-81; 1977.

The effect of RU 16117 (11 α -methoxy ethinyl estradiol) on the induction of mammary tumors in female Sprague-Dawley rats by dimethylbenz(a)anthracene (DMBA: 20 mg) by gastric gavage was investigated. From the first day that DMBA was administered, the rats received RU 16117 (0.5, 2, 8, or 24 $\mu\text{g}/\text{day}$ sc) or vehicle alone. All animals either died or had been killed by 130 days. Daily doses of 0.5 and 2 μg RU 16117 reduced tumor incidence to 78.6% and 40%, respectively. Doses of 8 or 24 $\mu\text{g}/\text{day}$ completely inhibited tumor development. Ovariectomy the day after DMBA treatment inhibited tumor appearance until day 95, when 2/14 animals developed tumors. The number of tumors per rat and the size of the tumors, but not the latency period, were also reduced by this treatment. Receptors for estradiol, progesterone, and prolactin in tumor tissue were reduced after 2 μg RU 16117, but binding of growth hormone and insulin was not affected. Although plasma luteinizing hormone levels decreased after 8 or 24 μg , plasma prolactin levels slightly increased in the animals receiving 24 μg . It is suggested that the potent inhibitory effect of RU 16117 on DMBA-induced mammary carcinoma is due to action at both the hypothalamic-pituitary and tumor (mammary gland) levels with the action at the peripheral level being secondary to reduced sensitivity of the tissue to circulating hormones through lowering of hormone receptor concentrations. (33 refs.)

- 77-6696 **Potent Inhibitory Effect of a New Antiestrogen (RU 16117) on the Growth of 7,12-Dimethylbenz(a)anthracene-induced Rat Mammary Tumors.** (Eng.) Kelly, P. A. (Medical Res. Council Group in Molecular Endocrinology, Le Centre Hospitalier de l'Universite Laval, Quebec GIV 4G2, Quebec, Canada); Asselin, J.; Caron, M. G.; Labrie, F.; Raynaud, J. P. *J Natl Cancer Inst* 58(3): 623-628; 1977.

At a dose of 24 $\mu\text{g}/\text{day}$ for 4 wk, RU 16117 (11 α -methoxyethinylestradiol), a new antiestrogen, led to a 65% reduction in the growth of dimethylbenz(a)anthracene (DMBA)-induced mammary tumors in female Sprague-Dawley rats. Both tumor number and tumor size were reduced by RU 16117 in a manner similar to that seen after ovariectomy. The absence of an inhibitory effect of doses of 0.1-12.5 $\mu\text{g}/\text{day}$ 17 β -estradiol (E_2), a range covering the low estrogenic activity of the RU 16117 doses, suggested that the inhibitory effect of RU 16117 was not due to its estrogenic activity. Decreased levels of receptors for E_2 , progesterone, and prolactin were found in the tumors remaining after ovariectomy; treatment with 24 μg of RU 16117 had a similar inhibitory effect on the E_2 and prolactin receptor levels. These data suggest that a reduction of hormone receptor levels in the tumor tissue was the mechanism by which RU 16117 inhibited the growth of the DMBA-induced mammary carcinomas. (31 refs.)

7-6697 The Activity of 7-Methylbenz(a)anthracene Metabolites in an In Vitro-In Vivo Carcinogenicity Test Using Mouse Lung Tissue. (Eng.) Flaks, A. (Cancer Res. Unit, Dept. Biology, Univ. York, Heslington, York YO1 SDD, England); Sims, P. *Cancer Lett* 3(3-4): 63-167; 1977.

The carcinogenicity of 7-methylbenz(a)anthracene (7-MBA), trans-5,6-dihydro-5,6-dihydroxybenz(a)anthracene, 7-MBA 5,6-oxide, and trans-8,9-dihydro-8,9-dihydroxy-7-MBA were tested. The test compounds were incubated for 1 hr with BALB/c mouse pulmonary tissue, which was then implanted into isologous mice. After 1 yr, the implants were removed and examined histologically. All four compounds produced a small number of adenomas; in addition, the 5,6-oxide produced two carcinomas. The results failed to provide conclusive evidence that any one of the compounds tested was more active than the other three. (19 refs.)

7-6698 Molecular Structure of the K-Region cis-Dihydrodiol of 7,12-Dimethylbenz(a)anthracene. (Eng.) Zacharias, D. E. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111); Glusker, K. P.; Harvey, R. G.; Fu, P. P. *Cancer Res* 37(3): 775-782; 1977.

The molecular structure and conformation of the cis-5,6-dihydrodiol of 7,12-dimethylbenz(a)anthracene (DMBA) were determined by x-ray crystallographic analysis. The compound crystallizes in the space group C_{2h}^2 with cell dimensions $a = 17.799$, $b = 33.211$, $c = 10.241$, $A, \beta = 91.88^\circ$. There are two molecules, designated I and II in the asymmetrical unit, that are not related to each other by crystallographic symmetry. The two conformations are almost identical, and there are no significant differences in their bond lengths or angles. In both molecules, the 5-hydroxyl group is equatorial and the 6-hydroxyl group is axial. This conformation is probably forced by steric hindrance between the hydroxyl group, O-6, and the hydrogen atoms of the 7-methyl group. The molecules pack in the crystal by forming hydrogen bonds between the hydroxyl groups of adjacent molecules. The ring system of the cis-5,6-dihydrodiol is much more buckled than that in DMBA. The angle between the two outermost rings is 36° , the deviation from planarity being primarily a consequence of partial saturation in the ring containing the two hydroxyl groups. Extrapolation of these results to other dihydrodiol derivatives of carcinogenic hydrocarbons permits predictions of preferred molecular geometry. Thus, the 8,9-dihydrodiol-10,11-epoxide of DMBA should probably exist preferentially in a conformation bearing the 8-hydroxyl group in the axial orientation. (38 refs.)

7-6699 Tumorigenicity of Five Dihydrodiols of Benz[a]anthracene on Mouse Skin: Excep-

tional Activity of Benz[a]anthracene-3,4-dihydrodiol. (Eng.) Wood, A. W. (Dept. Biochem. and Drug Metabolism, Hoffmann-La Roche, Inc., Nutley, N. J. 07110); Levin, W.; Chang, R. L.; Lehr, R. E.; Schaefer-Ridder, M.; Karle, J. M.; Jerina, D. M.; Conney, A. H. *Proc Natl Acad Sci* 74(8): 3176-3179; 1977.

The tumorigenicity of benz(a)anthracene (BA) and the 1,2-, 3,4-, 5,6-, 8,9-, and 10,11-dihydrodiols of BA were examined in female CD-1 mice. The compounds to be tested were applied to the shaved dorsal surface of the mice at a dose of 0.4, 1.0, or 2.0 μ mole. BA 3,4-dihydrodiol was the most active tumor initiator at all three doses, inducing 2.4, 3.6, and 4.8 papillomas/mouse at the three doses, respectively. None of the other dihydrodiols, at any dose, was more active than the parent compound. The high tumorigenicity of this metabolite was supportive of the bay region theory of polycyclic hydrocarbon carcinogenicity. BA produced only 0.14, 0.30, and 0.30 papillomas/mouse at the three doses, respectively. BA 1,2-dihydrodiol was the least active, producing only 0.04, 0.10 and 0.07 tumors/mouse at the three doses, respectively. The respective values for the other metabolites were as follows: BA 5,6-dihydrodiol: 0.07, 0.03, and 0.20; BA 8,9-dihydrodiol: 0.10, 0.07, and 0.21; BA 10,11-dihydrodiol: 0.13, 0.10, and 0.14. The first tumors appeared 12 to 18 wk after the start of the experiment. (27 refs.)

77-6700 Morphology, Histochemistry and Isozymes of Monkey Kidney Cells During Long-Term Exposure to Cigarette Smoke. (Eng.) Fleming, N. (Electron Microscopy Div., Dept. Anatomy, Univ. Zurich, Gloriastrasse 19, CH-8006 Zurich, Switzerland); Kistler, G. S. *Acta Histochem (Jena)* 60(1): 132-145; 1977.

Monkey kidney cells (Vero) in monolayer culture were exposed to 260 puffs of whole smoke from a mid-tar-range cigarette for 240 days. Cell morphology was investigated at the light and electron microscopic levels. The histochemical characteristics of several hydrolytic enzymes and dehydrogenases were examined, and the isozymes of lactate dehydrogenase, malate dehydrogenase and glucose-6-phosphate dehydrogenase were studied. For all these parameters, smoke-exposed cells displayed the same features as sham-exposed and negative controls. The cells were assessed as nonmalignant by their failure to induce tumors in nude mice. (23 refs.)

77-6701 Chemical Evaluation of the Beeswax Pellet Implantation Bioassay Model for Studies of Environmental Carcinogens. (Eng.) Rubin, I. B. (Bio/Organic Analysis Group, Analytical Chemistry Div., Oak Ridge Natl. Lab., Post Office Box X, Oak Ridge, TN 37830); Guerin, M. R. *J Natl Cancer Inst* 58(3): 641-644; 1977.

The release properties of constituents of cigarette smoke condensate in a condensate-beeswax matrix were characterized

by an in vitro study. Eighteen compounds representative of several classes of condensate components were tested. Equal quantities of condensate and beeswax, mixed with tracer quantities of ^{14}C -labeled test compounds, were formed into rod-shaped pellets similar to those used for trachea implant studies, and the rate at which the ^{14}C was removed from the pellet by a flowing saline stream was monitored. The results indicated a wide range in the release rates of the test compounds. The smaller and water-soluble molecules were released rapidly; about 90% of the nicotine and phenol was leached out in the first 24 hr. Larger and less-soluble molecules were released slowly or not at all. Only 10% of the stearic acid and essentially none of the benzo(a)pyrene was released in 28 days. The effects of such an uneven release of components from an implantation of biologically active material in an inert carrier matrix are discussed with regard to bioassay systems. (10 refs.)

- 77-6702 **Concentration of Mutagens from Urine by Adsorption with the Nonpolar Resin XAD-2: Cigarette Smokers Have Mutagenic Urine.** (Eng.) Yamasaki, E. (Biochemistry Dept., Univ. California at Berkeley, Berkeley, CA 94720); Ames, B. N. *Proc Natl Acad Sci USA* 74(8): 3555-3559; 1977.

A resin adsorption technique was developed for concentrating mutagens/carcinogens from human urine about 200-fold, and it was applied to the urine of cigarette smokers and nonsmokers for subsequent assay in the *Salmonella typhimurium*/mammalian microsome mutagenicity test. The urine (up to 500 ml) was put through a column with a 1.5-cm³ bed volume of XAD-2 (styrene-divinylbenzene polymer), and the adsorbed material was eluted with acetone. The acetone was taken to dryness and the residue dissolved in dimethyl sulfoxide to give a urine concentrate that was then assayed in the mutagenicity test. The 37 urine samples from 21 nonsmokers examined on *Salmonella* strain TA1538 showed no significant mutagenicity; a few samples showed weak activity on strain TA100. All seven smokers who inhaled and smoked ordinary cigarettes had significant mutagenic activity in their urine. In eight smokers, the night urine showed more activity than the morning urine. Two smokers who did not inhale showed no significant mutagenic activity. It is proposed that this method be used to examine the urine of a large population of nonsmokers in order to detect unsuspected mutagens/carcinogens and to examine particular populations that are likely to be absorbing significant doses of mutagens. The method may also be used to monitor experimental animals in toxicological studies and to determine the mutagenicity of water pollutants and other aqueous fluids. (38 refs.)

- 77-6703 **Studies on the Local and Systemic Carcinogenicity of Topically Applied Smoke Condensate from a Substitute Smoking Material.** (Eng) Clapp, M. J. (Central Toxicology Lab., Imperial Chemical Indus-

tries Ltd., Alderley Park, Macclesfield, Cheshire SK10 4TJ, England); Conning, D. M.; Wilson, J. *Br J Cancer* 35(3): 329-341; 1977.

The topical carcinogenicity to mouse skin of smoke condensates from a tobacco substitute, alone or in combination with tobacco, was compared with that of a tobacco condensate and acetone, the solvent used. The tobacco substitute (NSM) contained cellulose, sodium carboxymethyl cellulose, glycerol, calcium carbonate, magnesium carbonate, bentonite, and ammonium sulfate. Sixteen types of cigarettes were used to make the condensates, and the age standardized results were analyzed according to the Weibull distribution model. The NSM condensate had < 25% of the potency of the tobacco condensate (37% at 95% upper confidence limit), and condensates from blends of NSM and tobacco were similarly reduced in activity. Histopathological examination of normal and tumorous skin sections and an analysis of the incidence of skin hyperplasia failed to reveal any abnormalities due to NSM. (15 refs.)

- 77-6704 **Action of Cigarette Smoke Condensate on the Initial Stage of Morphogenesis of the Chicken Lung In Vitro.** (Fre) Guimard, J. (Laboratoire de Biologie-Vertebres, Universite de Paris-Sud, 91405 Orsay, France). *C R Soc Biol (Paris)* 171(3): 553-559; 1977.

The action of cigarette smoke condensate on the initial stage of morphogenesis of the chicken lung was studied in tissue cultures from 5.5- to 6-day-old embryos. The condensate was obtained from filterless cigarette smoke according to the CORESTA Standard; the smoke was condensed at -80°C. Morphological studies were carried out after 3 days' incubation. Judged by the retarded branching of the mesobronchus, treatment of the mesenchyma with the condensate inhibited mesenchymal induction. The cigarette smoke condensate reduced the mitotic activity of the mesenchyma significantly compared with control cultures (10.42/1,000 cells vs 12.20/1,000 cells). Epithelial competency, however, did not seem impaired. (19 refs.)

- 77-6705 **The Effects of Some Tobacco Smoke Constituents on Foreign Compound Metabolism in the Cat and the Rat.** (Eng) Turner, D. M. (Dept. Biochemistry and Drug Metabolism, Hazleton Labs. Europe Ltd., Otley Road, Harrogate, N. Yorkshire, England). *Res Commun Chem Pathol Pharmacol* 16(3): 425-442; 1977.

The effects of chronic nicotine administration on its own metabolism were studied in female cats and male Wistar rats. The rats received three sc injections of 0.4 mg/kg nicotine daily from 2 wk; the cats were inoculated iv with 2 µg/mg every 60 sec, 12 hr/day, for a max of 24 wk. Nicotine increased the in vitro metabolism in the liver of both species and in the cat kidney. Cotinine production from nicotine was enhanced in both species by pretreatment with nicotine. The

magnitude of the increase in enzyme activity was relatively small but of the same order as that produced in the rat by phenobarbital (37.5 mg/kg, ip). 3-Methylcholanthrene (20 mg/kg, ip) pretreatment stimulated rat liver nicotine metabolism but had no effect on cotinine production. Chronic exposure of rats to relatively low levels of carbon monoxide inhibited the in vitro aryl hydrocarbon hydroxylase activity but did not affect nicotine metabolism (38 refs.)

77-6706 A Study of Tobacco Carcinogenesis. XV. Effects of N'-Nitrosonornicotine and N'-Nitrosoanabasine in Syrian Golden Hamsters. (Eng.) Hilfrich, J. (Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, New York 10595, U.S.A.); Hecht, S. S.; Hoffmann, D. *Cancer Lett (Amsterdam)* 2: 169-76; 1977.

The carcinogenic activity of N'-nitrosonornicotine (NNN) and N'-nitrosoanabasine (NAB) in Syrian golden hamsters was studied. Four groups of hamsters (10 male, 10 female in each group) were treated as follows: Group I was given 1% NNN, single dose 5 mg, total dose 375 mg; Group II was given 1% NAB, single dose 5 mg, total dose 375 mg; Group III, positive control group, was given 0.4% N-nitrosopiperidine (NPD) single dose 2 mg, total dose 150 mg; Group IV, negative control group, was given saline solution. All animals were injected sc three times a wk for 25 wk. Histologic examination at 83 wk revealed no neoplastic changes in negative controls and NAB-treated animals. However, 12 of the 19 NNN-treated hamsters developed tracheal tumors, and one developed carcinoma of the nasal cavity. All NPD-treated animals exhibited multiple tracheal tumors; in addition, 50% showed neoplasms of the nasal cavity. By comparison with the relatively strong carcinogen NPD, NNN was moderately active in the upper respiratory tract, while NAB had no effect. This supports the concept that NNN is related to the increased incidence of cancer in tobacco smokers and chewers. (27 refs.)

77-6707 Kinetics of Nornicotine and Anabasine Nitrosation in Relation to N'-Nitrosonornicotine Occurrence in Tobacco and to Tobacco-induced Cancer. (Eng.) Mirvish, S. S. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NB 68105); Sams, J.; Hecht, S. S. *J Natl Cancer Inst* 59(4): 1211-1213; 1977.

The kinetics of nornicotine (NN) and anabasine (AB) nitrosation were studied in aqueous solution. The kinetics were similar to those of other aliphatic secondary amines, with third-order stoichiometric rate constants of 1.15 and 0.86 $M^{-2} \text{ sec}^{-1}$ for NN and AB, respectively. The data also indicated that N'-nitrosonornicotine in tobacco arises from nicotine and that NN and AB in tobacco and

tobacco smoke can be nitrosated in vivo to the corresponding carcinogenic nitrosamines. (16 refs.)

77-6708 Enzyme Histochemical Pattern of Hepatic Glycogen Storage Foci During NNM Carcinogenesis (Meeting Abstract). (Eng.) Hacker, H. J. (Abteilung Cytopathologie, Inst. Experimental Pathology, Deutsches Krebsforschungszentrum, D-6900 Heidelberg, W. Germany); Bannasch, P. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977.* International Agency for Research on Cancer. (Lyon, France): p. 83; 1977. (no refs.)

77-6709 Hepatic Glycogenosis and Activity of Some Related Enzymes in Early Stages of NNM Carcinogenesis (Meeting Abstract). (Eng.) Mayer, D. (Abteilung Cytopathologie, Inst. Experimental Pathology, Deutsches Krebsforschungszentrum, D-6900 Heidelberg, W. Germany); Bannasch, P. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977.* International Agency for Research on Cancer. (Lyon, France): p. 82; 1977. (no refs.)

77-6710 Development of Tumors in the Glandular Stomach of Rats after Oral Administration of Carcinogens. II. Different Cell Types in Antral Carcinoma as Revealed by Electron Microscopy. (Eng.) Uchida, Y. (Dept. Surgery, Nagasaki Univ. Sch. Medicine, Sakamoto-machi 7-1, 852 Nagasaki, Japan); Roessner, A.; Schlake, W.; Ruhland, D.; Themann, H.; Grundmann, E. *Z Krebsforsch* 87(2): 213-228; 1976.

Experimental tumors of the glandular stomach of rats were examined electron microscopically to identify the different cell types found in the carcinoma and to clarify the possible relationship between the undifferentiated carcinoma cells and the more differentiated cell types seen. The tumors were induced by the po administration of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) for 8 or 35 wk or N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) for 20 wk. In addition to undifferentiated carcinoma cells, several differentiated cell types such as goblet cells, endocrine cells, cells with lamellated inclusions in their cytoplasm, and squamous carcinoma cells were observed. Carcinomatous gland cells with well-differentiated microvilli on their luminal surface and typical tonofilamentous structures in their cytoplasm were seen. These cells exhibited properties of squamous epithelium and of gland cells and may be considered as intermediate variants between adenocarcinoma cells and squamous carcinoma cells. The finding of these intermediate variant cells suggests the possibility of differentiation by cell division of adenocar-

cinoma cells into several types of well-differentiated carcinoma cells in the glandular stomach of rats undergoing MNNG or ENNG carcinogenesis. (36 refs.)

- 77-6711 Development of Tumors in the Glandular Stomach of Rats after Oral Administration of Carcinogens. I. Histological Findings.** (Eng) Uchida, Y. (First Dept. Surgery, Nagasaki Univ. Sch. Medicine, Sakamoto-machi 7-1, 852 Nagasaki, Japan); Schlake, W.; Roessner, A.; Ruhland, D.; Themann, H.; Grundmann, E. *Z Krebsforsch* 87(2): 199-212; 1976.

Histological patterns in the rat stomach were determined at different intervals during carcinogenesis induced by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG; 150 mg/liter po) for 35 wk or by N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG; 500 mg/liter po) for 20 wk. Rats were killed at various intervals from 1 to 35 wk after the start of treatment and specimens examined histologically and histochemically. Several dysplastic reactions were observed in the antral mucosa during tumor development. The first, regenerative hyperplasia, was seen 1-9 wk after administration of MNNG and was characterized by irregular glandular proliferations at the margin of erosions and ulcers. After 12-17 wk, glandular hyperplasia involved the extension of either crypts or glands and the thickening of mucosal layers. At this stage there were still no signs of cell atypia. Dysplasia occurred after 21-35 wk and was combined with considerable structural modification and cellular atypia. This lesion, however, was limited to the mucosal layer. Neoplastic changes were characterized by marked cellular atypia and extension to tunica submucosa and tunica serosa. Some tumors showed benign histological patterns, but most were adenocarcinomas. Metastases into pancreas, liver, lymph nodes, and ribs were observed. No particular enzyme patterns were found by histochemistry. The precancerous role of intestinal metaplasia in the glandular stomach of carcinogen-treated rats could not be confirmed by these results. (22 refs.)

- 77-6712 Promoting Effect of Bile Acids in Colon Carcinogenesis in Germ-free and Conventional F344 Rats.** (Eng) Reddy, B. S. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595); Watanabe, K.; Weisburger, J. H.; Wynder, E. L. *Cancer Res* 37(9): 3238-3242; 1977.

Tumor incidence in female F344 germ-free and conventional rats treated with individual bile acids and/or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) was studied. Rats received intrarectal instillations of MNNG for 2 wk (total dose, 8 mg/rat) and then sodium cholate (sc) or sodium chenodeoxycholate (SCDC) (20 mg/rat/dose) three times a wk for 46 wk; MNNG for 2 wk and vehicle alone for 46 wk; or bile acids alone for 48 wk. No tumors were found in germ-free

rats given SC or SCDC alone. However, colon tumors were found in rats treated with MNNG and SC or SCDC. The bile acids increased MNNG-induced adenocarcinomas and adenomas in germ-free rats and MNNG-induced adenomas in conventional rats. Conventional rats treated with MNNG and SC or SCDC had a higher incidence ($p < 0.05$) of colon tumors than those given MNNG alone. Germ-free rats treated with MNNG and bile acids had a slightly higher incidence of colon tumors than those given MNNG alone. The increase in tumor production with SC or SCDC in conventional rats is probably due to the production of deoxycholic acid or lithocholic acid by bacterial 7 α -dehydroxylation in the colon. It is concluded that SC and SCDC promoted MNNG-induced colon carcinogenesis in rats. (31 refs.)

- 77-6713 Adenomatous Changes and Adenocarcinoma of Glandular Stomach in Wistar Rats Induced by N-Methyl-N'-nitro-N-nitrosoguanidine: An Electron Microscopic and Histochemical Study.** (Eng) Kobori, O. (First Dept. Surgery, Faculty Medicine, Univ. Tokyo, 7-3-1 Hongo Bunkyo-Ku, Tokyo 113, Japan); Gedigk, P.; Totovic, V. *Virchows Arch [Pathol Anat]* 373(1): 37-54; 1977.

The evolution of gastric carcinoma was studied in Wistar rats given N-methyl-N'-nitro-N-nitrosoguanidine (MNNG, 80 μ g/ml) in their drinking water for 7 mo. Of the 39 rats that survived beyond the treatment period, 92% developed cancer, including 1 early carcinoma and 35 invasive carcinomas. Two adenomas and two benign regenerative lesions were also observed. Similar to a previous study, almost all the benign and malignant lesions were located near the midpoint of the lesser curvature. The combined results of both studies indicate that benign erosions develop after 5 wk of MNNG feeding and that the erosion process progresses to adenomatous growth and then to early carcinoma between 25 and 35 wk. Subsequently, the carcinoma infiltrates the muscularis propria and subserosa. Electron microscopy showed that the adenomas and carcinomas consisted predominantly of undifferentiated cells with poorly developed cytoplasmic organelles. Histochemically, both showed strongly positive reactions for lysosomal enzymes. The malignancy of the carcinomas was confirmed by their successful transplantation to syngeneic animals. (27 refs.)

- 77-6714 Induction of Liver Tumors in Rats by Sodium Nitrite and Methylguanidine.** (Eng) Matsukura, N. (Biochemistry Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo, Japan); Kawachi, T.; Sasajima, K.; Sano, T.; Sugimura, T.; Ito, N. *Z Krebsforsch* 90(1): 87-94; 1977.

The carcinogenicity of sodium nitrite and methylguanidine, singly and together, was examined in Wistar rats. Among 15 rats continuously fed a pellet diet containing 0.16% sodium nitrite and 0.16% methylguanidine, there

ere 6 liver hemangiomas, 8 bile duct adenomas, and malignant tumors (hepatocellular carcinoma, hemanosarcoma, and spindle cell sarcoma). Two hemangiomas and 2 bile duct adenomas were found in 4 rats and a pellet diet containing 0.16% sodium nitrite. Only 1/5 rats fed pellets containing 0.16% methylguanidine developed a hemangioma. No tumors developed in the controls. All the tumors occurred in rats that survived for > 12 months. No significant changes were detected in the esophagus and stomach. (13 refs.)

77-6715 Formation of Nitrosamines in the Human Digestive Tract. Evolution of pH and of Nitrate and Nitrite Concentrations in the Gastric Juice During Digestion. (Fre.) Klein, D. (Department de Nutrition et des maladies metaboliques, Universite de Nancy I, 40, rue Sanguin, 54000 Nancy, France); Gaconnet, N.; Beaufrand, J. J.; Debray, G. *Ann Nutr Aliment* 30(5/6): 813-821; 1976.

Nitrate and nitrite concentrations and pH changes were monitored during digestion in three healthy subjects who received food containing 3.5 mM of nitrate and 0.020 mM nitrite via a nasal tube. Stomach contents were taken later for determination of nitrite, nitrate, and pH according to the method of Geiss. At the start of digestion, the pH was 5.3 and the respective concentrations of nitrite and nitrate were 2.7 and 0.006 mM. The pH diminished linearly and 95 min after the intake of food it reached 3.12. The nitrate level also dropped, to 1.76 mM, but the nitrite level increased with time of digestion and acidity to 0.01 mM. The trial suggests that the main source of nitrite in the stomach comes from reduction of nitrates ingested with food. (11 refs.)

77-6716 Formation of Nitrites from Nitrates in the Digestive Tract. (Fre.) Fritsch, P. (Groupe de Recherches sur la toxicologie des aliments et des boissons, INSERM, U 87, Universite Paul-Sabatier, Institut de Physiologie, 2, rue Francois-Magendie, 31400 Toulouse, France); Le Saint-Blanquat, G. *Ann Nutr Aliment* 30(5-6): 793-804; 1976.

The results of in vitro anaerobic incubation of rat gastric mucosa in the presence of nitrates are presented. Nitrate and nitrite contents in the various media were quantified. The findings suggest that nitrates are reduced to nitrites specifically by ileo-cecal microflora and, perhaps to a lesser degree, by the action of a nitrate reductase in the gut. In situ nitrate perfusion (400 mg/liter) of the small intestine showed that nitrate absorption is very rapid but that these nitrates do not accumulate in the blood. The evidence indicates a possible nitrate reduction in the intestinal gut. (40 refs.)

77-6717 Inhibition of Amine-Nitrite Hepatotoxicity by α -Tocopherol. (Eng) Kamm, J. J. (Roche Res.

Center, Nutley, NJ 07110); Dashman, T.; Newmark, H.; Mergens, W. J. *Toxicol Appl Pharmacol* 41(3): 575-583; 1977.

In vivo and in vitro experiments were performed to determine the effect of α -tocopherol, α -tocopherol-quinone, and γ -tocopherol on nitrite toxicity. Experiments to determine the role of pH were conducted with α -tocopherol only. At pH 2 or 3, nitrite anion was rapidly lost from reaction mixtures containing 8.0 mM α -tocopherol and 7.0 mM nitrite. As the pH increased, the reaction slowed until at pH 5, about 90% of the nitrite remained after 50 min. α -Tocopherol reacts more readily than ascorbate to destroy nitrite anion below pH 4. All three compounds were tested (8.0 mM) in simulated gastric juice: both α - and γ -tocopherol caused a rapid loss of nitrite anion from the reaction mixture, but α -tocopherol-quinone had no effect. The latter may be a reaction product, since it increased as nitrite anion decreased. The elevation in SGPT normally observed upon treatment of animals (male Sprague-Dawley rats) with 0.43 mM sodium nitrite and 0.15 mM aminopyrine was eliminated when 0.06, 0.13, 0.26, or 0.51 mM α -tocopherol was included in the regimen. The protective effect was dose-related. Further evaluation indicated that the highest dose of α -tocopherol blocked the nitrosative cleavage of the amine to dimethylnitrosamine in the stomach. In similar experiments with 0.51 mM γ -tocopherol and α -tocopherol-quinone, the former, but not the latter, also exerted a protective effect. The significance of these findings for human toxicity is unknown. (24 refs.)

77-6718 Photolysis of Volatile Nitrosamines at the Pico-gram Level as an Aid to Confirmation. (Eng) Doerr, R. C. (Eastern Regional Res. Center, Agricultural Res. Service, U.S. Dept. Agriculture, Philadelphia, PA 19118); Fiddler, W. *J Chromatogr* 140(3): 284-287; 1977.

A method for determining whether peaks seen by gas-liquid chromatography-thermal energy analysis are nitrosamines was developed based on the rapid and complete photolytic decomposition of these compounds by 366 nanometer UV light. This method allows confirmation of nitrosamine presence when the quantities are too small for mass spectral confirmation. (15 refs.)

77-6719 Enzymatic Conversion of Benzo(a)pyrene Phenols, Dihydrodiols and Quinones to Sulfate Conjugates. (Eng) Nemoto, N. (Dept. Experimental Pathology, Cancer Inst., Toshima, Tokyo, Japan); Takayama, S.; Gelboin, H. V. *Biochem Pharmacol* 26(19): 1825-1829; 1977.

The enzymatic conjugation of oxygenated benzo(a)pyrene (BP) metabolites with sulfate was studied. The metabolites, at 1.25×10^{-4} M, were added to reaction mixtures containing 40 mM Tris-HCl, 100 μ g of 105,000 g supernatant protein

from rat livers, 5 mM MgCl₂, 5 mM ATP, and 2 mM ³⁵S-Na₂SO₄. The enzyme reaction was stopped with ethanol, and portions of aliquots were applied to Silica gel thin-layer sheets. All the BP phenol and quinoline metabolites tested formed conjugates with sulfate, as did three dihydrodiol metabolites. The 7,8-oxide showed the highest degree of sulfate conjugation; but the K-region oxide, 4,5-oxide, was a poor substrate. Only trace amounts of conjugate formed with the diol-epoxides I and II. (17 refs.)

- 77-6720 **A New Type of Biological Chemiluminescence: The Microsomal Chemiluminescence of Benzo(a)pyrene Arises from the Diol Epoxide Product of the 7,8-Dihydrodiol.** (Eng) Hamman, J. P. (McCollum-Pratt Inst., Johns Hopkins Univ., Baltimore, MD 21218); Gorby, D. R.; Seliger, H. H. *Biochem Biophys Res Commun* 75(3): 793-798; 1977.

The chemiluminescence (CL) accompanying the metabolism of benzo(a)pyrene (BP) by the aryl hydrocarbon hydroxylase system in the presence of rat liver microsomes was investigated. The CL was not inhibited by sodium dismutase nor by catalase, required molecular oxygen, and was substrate-specific. Both BP and 3-OH-BP exhibited the same quantum yield for microsomal CL, indicating that the production of 3-OH-BP from BP does not result in CL; a different reaction is involved. The quantum yield of CL from 7,8-dihydrodiol-BP was three times that of BP. The reactive metabolite was identified as the strongly mutagenic 7,8-dihydrodiol-9,10-epoxide, produced enzymatically from the 7,8-dihydrodiol precursor. Both (-) 7,8-dihydrodiol-BP and racemic 7,8-dihydrodiol-BP have the same microsomal chemiluminescent quantum yields, but the racemic diol CL shows a much higher initial intensity. The faster rate indicates a more rapid reaction with molecular oxygen, which is consistent with the much higher chemical reactivity reported for diol epoxide I produced from (+) 7,8-dihydrodiol-BP compared to diol epoxide II produced from the (-)diol. The CL resulting from the oxidation of BP by microsomes is therefore a specific adventitious biological CL of a mutagenically active diol epoxide metabolite. It appears that, for BP at least, the intensity and kinetics of microsomal CL may be used to follow the enzyme activities and pathways leading to the production of the highly mutagenic and presumably carcinogenic diol epoxides. (30 refs.)

- 77-6721 **Mutagenicity of Isomeric Diol-Epoxides of Benzo(a)pyrene and Benz(a)anthracene in *S. typhimurium* TA98 and TA100 and in V79 Chinese Hamster Cells.** (Eng) Malaveille, C. (International Agency Res. Cancer, 150 Cours Albert Thomas, F-69008 Lyon, France); Kuroki, T.; Sims, P.; Grover, P. L.; Bartsch, H. *Mutat Res* 44(3): 313-325; 1977.

Two pairs of isomeric vicinal diol epoxides from benzo-

[a]pyrene (BP: 7-β,8α-dihydroxy -9β,10β- epoxy-7,8,9,10-tetrahydrobenzo[a] pyrene and 7β,8α-dihydroxy -9α,10α- epoxy-7,8,9,10-tetrahydrobenzo[a] pyrene; 9β,10α-dihydroxy-7α,8α-epoxy -7,8,9,10- tetrahydrobenzo[a] pyrene and 9β,10α-dihydroxy -7β,8β- epoxy-7,8,9,10-tetrahydrobenzo[a] pyrene) and one pair of isomeric vicinal diol epoxides from benz[a]anthracene (8β,9α-dihydroxy-10β,11β-epoxy -8,9,10,11- tetrahydrobenz[a]anthracene and 8β,9α-dihydroxy -10α,11α- epoxy -8,9,10,11- tetrahydrobenz[a]anthracene) were tested for their ability to induce mutations in *Salmonella typhimurium* strains TA98 and TA100 and in V79 Chinese hamster cells. The diol concentrations ranged from 0 to 100 nanomoles per plate. All six diol epoxides were active in both bacterial strains, but the 9β,10β(syn)isomer of BP was considerably more mutagenic than the other diol epoxides. For the three pairs of stereoisomers, the ratio of the mutagenic potencies of the syn over the anti isomers varied with both chemical structure and bacterial strain. In the V79 cells, the two BP 7,8-diol 9,10-oxides were mutagenic, with the anti isomer being more potent; the reverse was true in *S. typhimurium*. The other four compounds were non mutagenic in V79 cells at the concentrations tested. (37 refs.)

- 77-6722 **Epidermal Hyperplasia after Topical Application of Benzo(a)pyrene Diol Epoxides, and Other Metabolites.** (Eng) Bresnick, E. (Dept. Biochemistry, Univ. Vermont Sch. Medicine, Burlington, VT 05401); McDonald, T. F.; Yagi, H.; Jerina, D. M.; Levin, W.; Wood, A. W.; Conney, A. H. *Cancer Res* 37(4): 984-990; 1977.

The effects of 0.2-1.2 micromoles of benzo(a)pyrene (BP) or 22 of its derivatives on the number of nuclei per unit length of epidermis, the number of cell layers of epidermis, and the thickness of the epidermal layer were studied in female C57BL/6J mice. Several BP derivatives induced hyperplasia that is typical of those produced by agents that promote skin tumorigenesis after application of an initiator. The most potent compounds were the BP diol epoxides (±) -7β,8α- dihydroxyl -9β,10β- epoxy-(1)7,8,9,10-tetrahydrobenzo(a)pyrene (diol epoxide 2) and (±) 7β,8α,8α-dihydroxy -9α,10α- epoxy -7,8,9,10-tetrahydrobenzo(a)pyrene (diol epoxide 2). These derivative were followed in activity by 9-hydroxy-benzo(a)pyrene (9-OH-BP), 2-hydroxybenzo(a)pyrene, and 9,10-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene. Since diol epoxide 1 and 9-OH-BP are noncarcinogenic, the results indicate that there is no strict correlation between the ability of BP derivatives to induce mutations and tumors and their ability to induce morphological alterations. The spectrum of epidermal BP metabolites apparently includes promoters, initiators, and complete carcinogens. (48 refs.)

- 77-6723 **In Vitro Reaction of Radioactive 7β,8α Dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahy**

benzo(a)pyrene and 7 β ,8 α -Dihydroxy-9 β , 10 β -epoxy-8,9,10-tetrahydrobenzo(a)pyrene with DNA. (Eng) Jensen, J. (Dept. Biochemistry and Molecular Biology, Univ. Florida, Box J245, JHMHG, Gainesville, FL 32610); Marina, D.; Yagi, H.; Cerutti, P. *Biochem Biophys Res Commun* 74(3): 934-940; 1977.

The in vitro reaction of bacteriophage T7-DNA with ³H-labeled diastereomeric benzo(a)pyrene (BP) diol oxides 7 β ,8 α -dihydroxy-9 α ,10 α -epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (BP diol epoxide I) and 7 β ,8 α -hydroxy-9 β ,10 β -epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene (BP diol epoxide II) was investigated. The two diastereomers formed distinct DNA adducts that could be readily separated by Sephadex LH-20 chromatography. These results, together with evidence from the literature, indicate that BP diol epoxide I leads primarily to the formation of N₂-[10-(7 β ,8 α ,8 α -trihydroxy-8,9,10-tetrahydrobenzo(a)pyrene)yl] deoxyguanosine, and BP diol epoxide II to N₂-[10-(7 β ,8 α ,9 β -trihydroxy-8,9,10-tetrahydrobenzo(a)pyrene)yl] deoxyguanosine. DNA-BP adducts with the same chromatographic properties were formed in mouse embryo fibroblasts upon treatment with BP. (14 refs.)

77-6724 **Excision Repair of Benzo(a)pyrene-Deoxyguanosine Adducts in Baby Hamster Kidney 21/C13 Cells and in Secondary Mouse Embryo Fibroblasts C57BL/6J.** (Eng) Shinohara, K. (Dept. Biochemistry and Molecular Biology, J. Hillis Miller Health Center, Univ. Florida, Gainesville, FL 32610); Cerutti, P. A. *Proc Natl Acad Sci USA* 74(3): 979-983; 1977.

Primary hamster kidney cells (BHK 21/C13) and C57BL/6J secondary mouse embryo fibroblasts (MEF) were incubated with radioactive ³H-benzo(a)pyrene (BP) at a final concentration of 0.33 μ g/ml of growth medium. DNA was extracted from the cultures and enzymatically hydrolyzed. Analysis of DNA by Sephadex LH-20 chromatography revealed two ³H peaks, one corresponding to N²-(10-[7 β ,8 α ,9 α -trihydroxy-8,9,10-tetrahydrobenzo(a)pyrene]yl)deoxyguanosine (dGua-BP I) and the other to the diastereomeric adduct N²-(10-[7 β , 8 α , 9 β -trihydroxy-7,8,9,10-tetrahydrobenzo(a)pyrene]yl)deoxyguanosine (dGua-BP II). The level of total dGua-BP in the BHK cells averaged 1.1 residues in 10⁶ deoxyribonucleosides. About 80% of the adducts in BHK cells were removed from DNA during a 72-hr treatment incubation. Deoxyguanosine arylalkylation was about 10 times higher in MEF than BHK cells, but excision occurred at a slower rate in MEF than in BHK. The persistence of these lesions at low toxicity may be relative to the carcinogenicity of BP. (32 refs.)

77-6725 **Benzo(a)pyrene Diol Epoxide Covalently Binds to Deoxyguanosine and Deoxyadenosine in**

DNA. (Eng) Meehan, T. (Lab. Chemical Biodynamics, Univ. California, Berkeley, CA 94720); Straub, K.; Calvin, M. *Nature* 269(5630): 725-727; 1977.

The adducts obtained by reacting 7 β ,8 α -dihydroxy-9 α ,10 α - epoxy -7,8,9,10- tetrahydrobenzo(a)pyrene [benzo(a)pyrene (BP) diol epoxide] with ³H-DNA were identified. Four differently labeled lots of DNA were synthesized in vitro with DNA polymerase I by incorporating in each case three unlabeled and one tritium-labeled nucleoside triphosphate. This labeling technique was used to demonstrate that activated BP forms two adducts with deoxycytidine, two with deoxyadenosine, and possibly one with deoxyguanosine. No reactions with deoxythymidine were detected. The high-resolution mass spectrum of the main deoxyguanosine adduct was consistent with a structure in which the 10-position of the hydrocarbon is attached to the N²-exocyclic amine of the base. Since the diol epoxide formed adducts only with bases containing a free amino group, it is possible that this is the hydrocarbon's preferred binding site. (22 refs.)

77-6726 **Benzo[a]pyrenedione/Benzo[a]pyrenediol Oxidation-Reduction Couples and the Generation of Reactive Reduced Molecular Oxygen.** (Eng.) Lorentzen, R. J. (Dept. Biochemical and Biophysical Sciences, Div. Biophysics, Johns Hopkins Univ., Baltimore, MD 21205); Ts'o, P. O. *Biochemistry* 16(7): 1467-1473; 1977.

The metabolism of benzo[a]pyrenes to the corresponding benzo[a]pyrenediones and the reduced benzo[a]pyrenediols was investigated. The results indicated that the benzo[a]pyrenediones are potentially harmful metabolites of benzo[a]pyrene which go through processes leading to their regeneration. These regenerative cycles in turn cause reactions with molecular oxygen; reactive reduced oxygen species are formed which may cause nucleic acid and cellular damage. (31 refs.)

77-6727 **Metabolic Activation of Benzo(a)pyrene and Binding to DNA in Cultured Human Bronchus.** (Eng) Yang, S. K. (Molecular Carcinogenesis Section, Chemistry Branch, NCI, NIH, Bethesda, MD 20014); Gelboin, H. V.; Trump, B. F.; Autrup, H.; Harris, C. C. *Cancer Res* 37(4): 1210-1215; 1977.

DNA binding levels were studied in cultured human bronchi exposed to 8 nanomoles of benzo(a)pyrene (BP) or its metabolites. The bronchial specimens were obtained from three lung cancer patients (1 adenocarcinoma and 2 squamous cell carcinomas) and from a patient who died of head trauma. The (-)-trans-7,8-diol of BP was more active in binding to DNA than BP and several of its metabolites, including phenols, (-)-trans-4,5-diol, and (-)-trans-9,10-diol. High-pressure liquid chromatography showed that the predominant metabolite formed from the (-)-trans-7,8-diol was the

diol epoxide r-7t,-8-dihydroxy-t-9,10-oxy-7,8,9,10-tetrahydrobenzo(a)pyrene. The results suggest that this diol-epoxide is the major metabolite bound to DNA in human bronchus. (38 refs.)

- 77-6728 **Benzo(a)pyrene Free-Radicals Formation in the Presence of Butylated Hydroxyanisole and Their Possible Importance in Carcinogenesis.** (Eng) Krzywanska, E. (Lab. Radiospectroscopy, Faculty Chemistry, Warsaw Univ., 02-092, Warsaw, Poland); Piekarski, L. *Neoplasma* 24(4): 395-400; 1977.

The electroparamagnetic resonance spectra of benzo(a)pyrene (BP) UV-irradiated in the presence of butylated hydroxyanisole (BHA) indicated the formation of a charge-transfer complex between 6-phenoxy-BP and BHA radicals. The reaction between BHA as the proton donor and the 6-phenoxy radical produced 6-hydroxy-BP and a neutral BHA radical. The reaction between 6-hydroxy-BP as the electron donor and the BHA radical gave the charge-transfer complex, in which BHA was in a semiquinone form. It is suggested that BHA-BPA radicals do not bind to DNA, which may explain the ability of BHA to reduce the carcinogenicity of BP. (16 refs.)

- 77-6729 **Formation of Benzo(a)pyrene-Glucuronic Acid Conjugates in Hamster Embryo Cell Cultures.** (Eng) Baird, W. M. (Wistar Inst. Anatomy and Biology, Philadelphia, PA 19104); Chern, C. J.; Diamond, L. *Cancer Res* 37(9): 3190-3197; 1977.

A major portion of the water-soluble metabolites of benzo(a)pyrene (BP) formed in hamster embryo cell cultures was determined to be glucuronic acid conjugates of BP phenols. Twenty-four hours after the addition of ^3H -BP [0.5 nanomole (nmol)/ml medium] to the cell cultures, > 80% of the ^3H -BP was metabolized. Most (90%) of the metabolites formed remained in the aqueous phase when the medium was extracted with an organic solvent. Treatment of the aqueous phase with β -glucuronidase converted at least 40% of the material into organic solvent-soluble derivatives. The converted material contained 33%-40% 9-OH-BP, 18%-21% 3-OH-BP, and 8%-11% BP quinones. The ratio of phenols to quinones was never greater than 7:1. Similar amounts of phenols and quinones were obtained by treating medium samples directly with β -glucuronidase. However, most BP metabolites in the organic solvent extract of the original medium were BP dihydrodiols. Cells exposed to 3-OH-BP formed a water-soluble product whose chromatographic behavior and spectra were identical with those of 3-OH-BP glucuronide. Cells exposed to ^3H -9-OH-BP (0.5 nmol/ml of medium) converted > 90% of this phenol to water-soluble derivatives in 24 hr, > 80% of which were then converted to ^3H -9-OH-BP by β -glucuronidase. Formation of glucuronic acid conjugates of

BP phenols is a major pathway of BP metabolism in hamster embryo cells in vitro. β -glucuronidase treatment of culture medium from these cells provides a way of determining the oxidation sites of more than one-third of the BP metabolites formed. (48 refs.)

- 77-6730 **Effects of Butylated Hydroxyanisole on the Metabolism of Benzo(a)pyrene by Mouse Liver Microsomes.** (Eng) Lam, L. K. (Dept. Lab. Medicine and Pathology, 456 Jackson Hall, Medical Sch., Univ. Minnesota, Minneapolis, MN 55455); Wattenberg, L. W. *J Natl Cancer Inst* 58(2): 413-417; 1977.

High-pressure liquid chromatography (HPLC) was used to analyze the metabolic profile of benzo(a)pyrene (BP) from incubations with liver microsomes prepared from butylated hydroxyanisole (BHA)-fed and control female A/HeJ mice. The BHA group was fed a diet containing 5 mg BHA/g commercial rat chow. The profile obtained showed that the peaks labeled BP-4,5-oxide and 1-hydroxybenzo(a)pyrene (1-HOBP) were present in much higher concentrations in the control run than in the BHA sample. To verify the validity of the HPLC, samples were simultaneously analyzed on thin-layer chromatography (TLC) plates under nitrogen. The radioactivity distribution of the four regions, diols, diones, HOBPs, and unreacted BP, on TLC was found to have well-defined peaks. Diol and dione formation decreased and HOBP formation increased in samples from BHA-fed mice, vs control samples. BP-4,5-oxide was later identified in the dione region. 3-HOBP was the major metabolite in both microsomal incubations; however, it was present in a significantly higher percentage in samples from the BHA-fed mice. This relative increase in 3-HOBP provides evidence of detoxification rather than activation. It was concluded that BHA produces two metabolic alterations in the mouse liver that could cause an inhibitory effect on BP-induced carcinogenesis. The first is an increase in 3-HOBP, a metabolite of detoxification, and the second is a decrease in epoxidation, which is an activation process. (22 refs.)

- 77-6731 **Phenols as Toxic Metabolites of Benzo(a)pyrene.** (Rus) Belitsky, G. A. (Lab. Chemical Carcinogenesis, Cancer Res. Center, Moscow, USSR); Ryabykh, T. P.; Koblyakov, V. A. *Tsitologiya* 19(10): 1193-1196; 1977.

The effect of benzo(a)pyrene (BP) and its phenol metabolites 3-hydroxybenzo(a)pyrene (3-OH-BP) and 6-hydroxybenzo(a)pyrene (6-OH-BP) on primary monolayer cultures of embryonal C3HA mouse fibroblasts and on transformed mouse (L cells) and hamster (874 cells) fibroblasts was studied. BP at 1 and 10 $\mu\text{g}/\text{ml}$ resulted in an approx twofold decrease in the number of embryonal fibroblasts, but it was noneffective against L and 874 cells. However, 3-OH-BP and, especially, 6-OH-BP almost completely inhibited growth of the cultures. The toxic effect of the metabolites did not change in the presence of the microsomal oxidase inhibi-

tor 7,8-benzo(a)flavone, and it was thus concluded that 3-OH-BP and 6-OH-BP do not require activation by nonspecific oxidases. (11 refs.)

77-6732 The Glutathione S-Transferase of the Small Intestine in the Rat. (Eng) Clifton, G. (Clinical Investigation Center, Naval Regional Medical Center, Oakland, CA 94627); Kaplowitz, N. *Cancer Res* 37(3): 788-791; 1977.

Glutathione S-transferase activity was investigated in the small intestine of three groups of Sprague-Dawley rats given either phenobarbital (8 mg/100 g ip daily for 10 days), 3,4-benzo(a)pyrene (1 mg ip bid for 10 days), or 3-methylcholanthrene (1 mg ip bid for 10 days). Two groups of animals were deprived of food for 24 and 48 hr, respectively. Three glutathione S-transferase activities were present in significant amounts in the small intestine with epoxide, p-nitrobenzyl chloride, and ethacrynic acid as substrates. The levels in the proximal intestine were higher than those in the middle or distal intestine, but they were significantly lower than those of the hepatic and renal transferases. Gel filtration and elution indicated that the three eluted as a single peak; there was no detectable binding to sulfobromophthalein. Transferase activities with the epoxide and p-nitrobenzyl chloride substrates were significantly reduced in the proximal and distal intestine after 48-hr starvation; with ethacrynic acid as a substrate, activity was affected only in the proximal segment. 3-Methylcholanthrene produced 33% and 37% increases of ethacrynic acid activity and 23% and 21% increases of p-nitrobenzyl chloride activity in the middle and distal intestines, respectively. Benzo(a)pyrene resulted in a 49% increase of ethacrynic acid activity in the distal intestine and 52% and 23% increases of p-nitrobenzyl chloride activity in the middle and distal segments, respectively. Phenobarbital induced 25% and 33% increases of p-nitrobenzyl chloride activity in the middle and distal intestine, respectively. There was no change in epoxide activity with any of the drug treatments. (30 refs.)

77-6733 Enhancement of Carcinogen Metabolism in Pregnant Mice and Their Embryos. (Rus) Shendrikova, I. A. (Lab. Biophysics, N. N. Petrov Scientific Res. Inst. Oncology, USSR Ministry Public Health, Leningrad, USSR); Ivanov-Golitsyn, M. N.; Likhachev, A. Ia.; Dikun, P. P. *Vopr Onkol* 23(4): 44-48; 1977.

The effect of an induction dose of benzo(a)pyrene (BP: 0.15-30 mg/kg iv), administered 24 hr before a second dose of BP (15 mg/kg, iv) or 9,10-dimethyl-1,2-benzanthracene (DMBA: 40 mg/kg, iv), on the metabolism of these carcinogens was studied in albino mice. The carcinogens were administered between days 19 and 21 of pregnancy. Metabolism was assessed by determining BP and DMBA concentrations in the maternal liver and fetus. Controls received no induction dose. Compared with controls, low induction doses re-

duced the BP concentration in the liver and fetus 15 min after the second dose of BP; the concentration was lowest with an induction dose of 0.75 mg/kg. Higher induction doses (7.5-15 mg/kg) increased BP levels, but the highest induction dose (30 mg/kg) also caused a reduction. Animals treated with DMBA were sacrificed 60 min later. Pretreatment with induction doses of BP had practically no effect on DMBA levels in the maternal liver and fetus. Study of the reduction of BP levels in the fetus as a function of time showed that an induction dose of 0.75 mg/kg did not influence the rate of reduction of the concentration, but it lowered the BP level considerably 5 min after administration of the second dose. The findings suggest the involvement of two different enzyme systems in BP metabolism: one is permanently present in the liver, while the other is induced by the carcinogen. The enzyme system activated by an induction dose of BP is unable to metabolize DMBA. (11 refs.)

77-6734 Fetal Rat Keratinizing Epidermal Cells in Culture: Effects of Long-Term Treatment by Benzo(a)pyrene on Their Growth Characteristics. (Eng.) Indo, K. (Dept. Pathology, Hyogo Medical Coll., 1-1, Mukogawa, Nishinomiya, Hyogo, Japan); Wilson, R. B. *J Natl Cancer Inst* 59(3): 867-880; 1977.

The effects of long-term treatment with benzo(a)pyrene (BP) were studied in vitro in near-term fetal MRC rat keratinizing epidermal cells. In untreated cells, temperatures of 30-32.5 C caused a cornification process in which thickened sheets of nearly pure keratinizing epidermal cells were formed. The mode of cellular differentiation in these sheets resembled in vivo cornification, with max growth at 30 C and lethality at 35 and 37.5 C. When cells treated with BP (2 or 0.2 µg/ml) were serially subcultured at 35 and 37.5 C, their original temperature sensitivity disappeared. In vitro sheet formation was accelerated (mitotic index of 30.7 vs only 0.9 in controls), and the BP-treated cell sheets continued to grow at elevated temperatures after the removal of BP. Pyknotic nuclei were noted, and back-transplantation into animals led to the formation of cysts surrounded by squamous epithelium. No tumorous growth at inoculation sites was noted for 6 mo. (30 refs.)

77-6735 The Triplet State of Benzo(a)pyrene as a Probe of Its Microenvironment in DNA Complexes. (Eng) Geacintov, N. E. (Chemistry Dept., New York Univ., New York, NY 10003); Moller, W.; Zager, E. In: *Excited States of Biological Molecules. Based on the Proceedings of the International Conference at the Calouste Gulbenkian Foundation Centre, Lisbon, Portugal, on April 18-24, 1974.* Birks, J. B., ed. (New York: John Wiley & Sons): 652 pp.; 199-206; 1976.

Flash photolysis techniques showed that the triplet lifetime of benzo(a)pyrene (BP) complexed with DNA in aqueous

solution was 20-80 times longer than that of BP in fluid benzene solution, whereas the quenching constant was approx 20 times smaller. This suggests that the BP molecule intercalated with DNA is located in a relatively viscous environment and is less accessible to other molecules. With pyrene-DNA complexes, the triplet state could not be detected, indicating that its lifetime is $< 50 \mu\text{sec}$. These results show that interactions in the aromatic hydrocarbon-DNA complexes are strongly dependent on the nature of the aromatic molecule. The triplet lifetime of the complexes may help to determine the mode of interaction of these molecules (many of which are carcinogenic) with nucleic acids. (22 refs.)

- 77-6736 Morphologic and Histochemical Characteristics of Cell Lines Derived from Hamster Peripheral Lung Tumors.** (Eng.) Kennedy, A. R. (Dept. Physiology, Harvard Sch. Public Health, Boston, MA 02115); McGandy, R. B.; Little, J. B. *Eur J Cancer* 13(11): 1341-1350; 1977.

The intratracheal instillation of the alpha emitter polonium-210 or benzo(a)pyrene in Syrian hamsters induces peripheral lung tumors that have a combined epidermoid and adenomatous morphology similar to that of human bronchiolar-alveolar carcinoma. Two permanent cell lines derived from these tumors have been studied in an attempt to determine the cell of origin of the original peripheral tumors. The ultrastructural and histochemical characteristics of both the cells and cheek pouch tumors grown from them at various stages of passage in tissue culture support, but do not prove, the hypothesis that the Clara cells in the terminal and respiratory bronchioles are the origin of the lung tumors induced in hamsters by these carcinogens. (31 refs.)

- 77-6737 Natural 3,4-Benzopyrene Content of Soil and Plant Samples of a Self-supporting Ecosystem.** (Hun.) Medve, F. (Debreceni Orvostudományi Egyetem Kozegeszsegtani és Jarvanytani Intezete, Debrecen, Hungary); Herman, K. *Egeszsegtudomány* 21(1): 76-79; 1977.

Soil and plant samples from a nonpolluted wooded area in Hungary were analyzed for 3,4-benzopyrene (BP) by a combination of thin-layer chromatography and spectrophotometry. BP levels in the upper soil layer were lowest in samples from the 5- to 10-cm and 90- to 100-cm depths (1.7 and 1.6 $\mu\text{g/kg}$, respectively) and highest in the 0- to 5-cm depth (3.4 $\mu\text{g/kg}$). The BP levels in plant samples ranged from 1.2 $\mu\text{g}/100 \text{ g}$ of dry sample in green oak leaves to 15 $\mu\text{g}/100 \text{ g}$ in decaying leaves. The results are in agreement with literature data. (12 refs.)

- 77-6738 Tissue Lesions of Tiger Salamanders (*Ambystoma tigrinum*): Relationship to Sewage Efflu-**

ents. (Eng) Rose, F. L. (Dept. Biological Sciences, Texas Tech Univ., Lubbock, TX 79409). *Ann NY Acad Sci* 298: 270-279; 1977.

A population of facultative neotenic tiger salamanders (*Ambystoma tigrinum*) inhabiting a sewage lagoon at Reese Air Force Base, Texas, was found to have a high rate of spontaneous tissue lesions. Neoplastic lesions originated in the epidermis, dermal fibroblasts or dermal melanophores; nonneoplastic lesions were also observed. The population consisted of an estimated 28,000 large, reproductively mature larvae that were restricted to the lagoon. Only 17% of the population metamorphosed normally. Polycyclic aromatic hydrocarbon analyses revealed traces of benzo(a)pyrene and high perylene concentrations (300 ppb) in the sludge. The results indicate that the low reported tumorigenic activity of perylene in mice and rats should be reevaluated. (24 refs.)

- 77-6739 Benzo(a)pyrene Metabolism in Human Embryonal Hepatocyte Culture.** (Rus) Belitsky, G. A. (Lab. Chemical Carcinogenesis, Cancer Res. Center, Moscow, USSR); Erizer, T. L.; Grinberg, K. N.; Khesina, A. Ya. *Vopr Onkol* 23(6): 69-73; 1977.

The microsomal oxidase activity in human liver cells was determined by exposing primary 5- and 11-day embryonal hepatocyte cultures growing in monolayer to benzo(a)pyrene (BP: 0.5 $\mu\text{g/ml}$). One, 2, 3, and 6 days later, the cells were removed and the carcinogen residue was assessed by spectral fluorescence. BP metabolism was significantly higher in the liver cells than in the fibroblast culture: the half-life of BP was approx 24 hr in the cells, compared with 72 hr in the fibroblasts. (14 refs.)

- 77-6740 Measurement of Benzo(a)pyrene Metabolism in Human Monocytes.** (Eng.) Lake, R. S. (Dept. Pathology, Children's Hosp. Medical Center Akron, Akron, OH 44308); Pezzutti, M. R.; Kropko, M. L.; Freeman, A. E.; Igel, H. J. *Cancer Res* 37(8, part 1): 2530-2537; 1977.

Measurement was made of the metabolism of tritiated benzo(a)pyrene (BP) to water-soluble metabolites by human monocytes derived from 5 ml of peripheral blood. Unlike BP metabolism in phytohemagglutinin (PHA)-stimulated lymphocytes, the specific metabolic activity of BP in the monocytes was found to be independent of PHA stimulation, of culture age up to 3 days, of 5%-20% fetal bovine serum levels in the culture medium, and of the initial concentration of the monocytes. One individual demonstrated coefficients of variation of specific metabolic activity of 7.3% when assayed by 10 independent tests on the same occasion, 9.03% when assayed eight times over a 3-mo period, and 11.8% when assayed four times on the same day. The assay is very sensitive, convenient, and less variable than

the similar lymphoblast assay: however, it may still be subject to fluctuation caused by donor status at the time of blood sampling. (29 refs.)

- 77-6741 **Metabolism of Benzo(a)pyrene by Guinea Pig Pancreatic Microsomes.** (Eng) Igbal, Z. M. (Sch. Public Health, Univ. Illinois Medical Center, Chicago, IL 60680); Varnes, M. E.; Yoshida, A.; Epstein, S. S. *Cancer Res* 37(4): 1011-1015; 1977.

The in vitro microsomal metabolism of the strain 13 guinea pig pancreas was investigated by determining benzo(a)pyrene (BP) hydroxylase activity in 9,000-g supernatants and microsomal pellets. BP hydroxylase activity in the supernatants and pellets was < 1% of the activity in the corresponding liver fractions. However, pretreatment of the animals with methylcholanthrene or BP at 20 mg/kg for 1 day or 3 consecutive days markedly enhanced the BP hydroxylase activity of pancreatic microsomes over that of control preparations. The induction in liver microsomes was less than twofold higher than that in the controls. BP hydroxylation by pancreatic microsomes was linear with time over a 30-min period, with the rate being dependent on both the enzyme and substrate concentrations. (29 refs.)

- 77-6742 **Comparison of the Tumor-initiating Activities of Benzo(a)pyrene Arene Oxides and Diol-Epoxides.** (Eng) Slaga, T. J. (Biology Div., Oak Ridge Natl. Lab., Post Office Box Y, Oak Ridge, TN 37830); Bracken, W. M.; Viaje, A.; Levin, W.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res* 37(11): 4130-4139; 1977.

The ability of arene oxides and diol epoxides of benzo(a)pyrene to initiate skin tumors in female CD-1 mice was determined in a two-stage system of tumorigenesis. BP 7 β ,8 α -diol-9 α ,10 α -epoxide was a much more effective tumor initiator than BP 7 β ,8 α -diol-9 β ,10 β -epoxide when applied topically in 0.2 ml of anhydrous dimethylsulfoxide:acetone (1:3) and then followed by twice-weekly applications of the promotor 12-O-tetradecanoylphorbol-13-acetate (10 μ g). BP 7 β ,8 α -diol-9 α ,10 α -epoxide was approx 20%-30% as active as BP as a tumor initiator. BP 7 β ,8 α -diol-7 β ,8 β -epoxide, BP 9,10-oxide, and BP 11,12-oxide possessed about 1%, 2% and 10%, respectively, of the tumor-initiating activity of BP. (30 refs.)

- 77-6743 **Induction of the Formation of New Hair Follicles in Mouse Tail Epidermis by the Tumor Promotor 12-O-Tetradecanoylphorbol-13-acetate.** (Eng) Schweizer, J. (German Cancer Res. Center, Inst. Biochemistry, Im Neuenheimer Feld 280, 6900 Heidelberg, W. Germany); Marks, F. *Cancer Res* 37(11): 4195-4201; 1977.

New hair follicle formation was quantitatively demonstrated in the tail skin of adult NMRI mice in a two-stage carcinogenesis experiment with 7,12-dimethylbenz(a)anthracene [100 nanomoles (nmol) in 100 μ l of acetone] as an initiator and 12-O-tetradecanoylphorbol-13-acetate (TPA, 20 nmol in 100 μ l of acetone) as a promoter, as well as in experiments with TPA alone. Two kinds of follicular neogenesis could be distinguished. The most frequent type was characterized by the organization of new follicles from the upper neck and orifice regions of existing follicles. During their development, these new follicles remained in close apposition to the original follicles but, after having reached a critical size, split off to form fully independent follicles. In the second type of follicular neogenesis, which occurred rarely, the new follicles seemed to arise directly from the epidermis between two sets of hair triads; however, these follicles never reached their final stage and did not produce hairs. The formation of new hair follicles may be explained by a dedifferentiation of epidermal cells caused by TPA. Because of the paucity and advanced stage of the papillomas that formed in the tail skin after long-term treatment with TPA, their derivation from the hair follicles could not be established. (34 refs.)

- 77-6744 **Ornithine Decarboxylase Induction and DNA Synthesis in Hamster Embryo Cell Cultures Treated with Tumor-promoting Phorbol Diesters.** (Eng.) O'Brien, T. G. (Wistar Inst. Anatomy and Biology, Philadelphia, PA. 19104); Diamond, L. *Cancer Res* 37(11): 3895-3900; 1977.

The effect of tumor-promoting phorbol diesters on ornithine decarboxylase (ODC) activity and DNA synthesis in normal and chemically transformed hamster embryo fibroblasts (HEF) in culture were studied. Only phorbol diesters with promoting activity in mouse skin induced ODC in HEF. ODC was induced in both cell types by 12-O-tetradecanoylphorbol-13-acetate (TPA). Max induction occurred 4-6 hr after addition of the promoter to the medium of confluent cultures, and it was greater in transformed cells than in normal cells. The extent of induction in transformed cells treated with 0.016-1.6 M TPA was dose-dependent. The cellular concentrations of polyamines, particularly putrescine, also increased after TPA treatment. The addition of TPA to confluent cultures of normal or transformed HEF did not increase cell number or the percentage of ³H-thymidine-labeled nuclei, nor did it stimulate ³H-thymidine incorporation. ODC also was induced by adding fresh medium to the cultures. When both fresh medium and TPA were added, the effect of the medium was markedly potentiated in transformed, but not in normal cells. These experiments demonstrate that tumor promoters specifically induce ODC in HEF without increasing DNA synthesis and that normal and transformed HEF differ in the levels of ODC activity attained after exposure to promoters. (20 refs.)

- 77-6745 **Effects of a Tumor-promoting Agent on Chondrogenesis.** (Eng) Pacifici, M. (Dept. Anatomy, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA 19174); Holtzer, H. *Am J Anat* 150(1): 207-212; 1977.

When exposed to the phorbol ester phorbol-12-myristate-13-acetate (PMA, 5×10^{-8} M), chondroblasts from 11-day chick cartilages lost their polygonal morphology within 6 hr and ceased to synthesize or accumulate the chondroblast-specific Type IV sulfated proteoglycan. This effect was reversible if the cells were kept in PMA for up to 72 hr. A longer exposure induced irreversible effects and resulted in a cell population that lacked the phenotypic properties of terminal chondroblasts. (10 refs.)

- 77-6746 **Effect of Phorbol Myristate Acetate on the Recovery of Spontaneous and Ultraviolet Light-induced 6-Thioguanine and Ouabain-resistant Chinese Hamster Cells.** (Eng) Trosko, J. E. (Dept. Human Development, Michigan State Univ., East Lansing, MI 48824); Chang, C. C.; Yotti, L. P.; Chu, E. H. *Cancer Res* 37(1): 188-193; 1977.

12-O-Tetradecanoylphorbol-13-acetate (TPA, 1 μ g/ml) and phorbol (0.59 μ g/ml) were tested in Chinese hamster cells for their effects on mutagenesis (resistance to 6-thioguanine and ouabain), DNA repair, and survival after UV irradiation (50, 100, 200 ergs/mm²). Recovery of 6-thioguanine- and ouabain-resistant colonies was significantly increased by TPA treatment and, to a lesser extent, by phorbol in UV-irradiated cells. Moreover, max enhancement of recoverable UV-induced 6-thioguanine- and ouabain-resistant mutants occurred when TPA was present after the mutation expression time and after the completion of DNA repair. This enhancement effect, while persisting up to 18 days in the 6-thioguanine mutation system, was max when TPA was applied about 2 days after UV irradiation for the ouabain-resistance mutation system. No significant decrease in cell survival was noted after post-UV treatment with TPA or phorbol, under conditions in which there was a slight but nonspecific inhibition of unscheduled DNA repair synthesis. These results do not support the hypothesis that the tumor promoting activity of TPA is due to its ability to inhibit error-free excision repair. However, the results are consistent with a two-stage hypothesis of carcinogenesis that includes mutational and epigenetic mechanisms to explain the initiation and promotion phases. (35 refs.)

- 77-6747 **The Effect of the Phorbol Ester Tumor Promoters on the Basal and Catecholamine-stimulated Levels of Cyclic Adenosine 3':5'-Monophosphate in Mouse Skin and Epidermis In Vivo.** (Eng) Mufson, R. A. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI 53706); Simsman, R. C.; Boutwell, R. K. *Cancer Res* 37(3): 665-669; 1977.

In vivo cyclic AMP levels in excised mouse skin are subject

to artifactual alterations unless the skin has been previously depilated. With this precaution, the cyclic AMP level in epidermal-dermal preparations from CD1 mice remained unchanged 1-18 hr after the topical application of 12-O-tetradecanoylphorbol-13-acetate [TPA, 17 nanomoles(nmol)]. However, the accumulation of cyclic AMP in response to isoproterenol (300 nmol, ip) or epinephrine (300 nmol) was significantly diminished 9-24 hr after TPA application. No enhanced accumulation of cyclic AMP in response to α -adrenergic stimulation accompanied this diminished β -adrenergic responsiveness. The tumor-promoting activity of various doses of TP and other phorbol esters was found to correlate with their ability to diminish the β -adrenergic responsiveness of the epidermis. (24 refs.)

- 77-6748 **Inhibition of Adipose Conversion of 3T3 Fibroblasts by Tumour Promoters.** (Eng) Diamond, L. (Wistar Inst. Anatomy and Biology, 36th at Spruce, Philadelphia, PA 19104); O'Brian, T. G.; Rovera, G. *Nature* 269(5625): 247-249; 1977.

The correlation between the ability of a phorbol ester to promote tumors in mouse skin and its ability to inhibit terminal differentiation of a clone of BALB/c 3T3 fibroblast cells (A31T preadipose cells) in culture was confirmed. 12-O-Tetradecanoyl-phorbol-13-acetate (TPA), phorbol-12,13-didecanoate (PDD), and phorbol-12,13-dibenzoate (PDB) completely inhibited adipose conversion at concentrations of 1.6×10^{-7} M, but the nonpromoters phorbol-12,13-diacetate (PDA), 4 α -PDD, and phorbol had no effect on conversion. Furthermore, the three promoters also enhanced the saturation density of the cell monolayers approx twofold, but the three nonpromoters had no effect on cell number. The inhibitory effects were not permanent. Conversion inhibition by TPA lasted for 14-18 days, that by PDD and PDB only 7 days. It is suggested that inhibition of terminal differentiation of cultured cells is a general property of tumor promoters, and that these compounds operate in vivo by interfering with normal differentiation. Inhibition of differentiation may give cells in which there is a potential for malignant change additional time to convert to tumor cells before becoming end cells. (18 refs.)

- 77-6749 **Investigations into the Mode of Action of the Cocarcinogen 12-O-Tetradecanoyl-phorbol-13-acetate Using Auxotrophic Bacteria.** (Eng.) Soper, C. J. (Dept. Pharmaceutics, Sch. Pharmacy, Univ. Bath, Claverton Down, Bath BA2 7AY, England); Evans, F. J. *Cancer Res* 37(8, part 1): 2487-2491; 1977.

An investigation was made of the effects of the cocarcinogen, 12-O-tetradecanoyl-phorbol-13-acetate (TPA), on mutagenesis in the *Salmonella typhimurium* histidine-requiring auxotrophs CS.281, CS.284, CS.285, and CS.288. CS.281 and CS.285 are reverted by single base-change substitutions, CS.284 and CS.288 by frameshift mutations; CS.285 and

CS.288 lack the excision repair system for DNA. TPA was not mutagenic or toxic to any of the test strains. At a concentration of 1 $\mu\text{g}/\text{ml}$, it had no effect on the reduction in cell viability produced by the mutagens *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) and 4-nitroquinoline 1-oxide (NQO), but the frequency of reversion to histidine independence induced by these mutagens was increased by factors of 3 for MNNG in strain CS.281 and 5.5 for NQO in CS.284. Enhancement of chemically induced mutation was also seen in the strains lacking excision repair, but the extent of enhancement was reduced in both cases. The results suggest that TPA may potentiate mutagenesis by chemical mutagens by altering the excision repair system. (16 refs.)

77-6750 Induction of Cell Division in BALB/c-3T3 Cells by Phorbol Myristate Acetate or Bovine Serum: Effects of Inhibitors of Cyclic AMP Phosphodiesterase and $\text{Na}^+\text{-K}^+\text{-ATPase}$. (Eng.) Sivak, A. (Aurhur D. Little, Inc., Acorn Park, Cambridge, MA 02140). *In Vitro* 13(6): 337-343; 1977.

The tumor promoter phorbol myristate acetate (PMA) or bovine serum stimulated cell division in BALB/c-3T3 mouse embryo cells. cAMP metabolism was found to be of critical importance for this induction of cell division, along with cAMP-phosphodiesterase activity. The addition of dibutyryl cyclic AMP (dbcAMP, 10^{-3} M) or other inhibitors of cAMP phosphodiesterase, such as papaverine (6.8×10^{-6} M), Persantin (5×10^{-5} M) or RO-20-1724 (10^{-4} M) prevented PMA- or serum-induced cell replication. However, ouabain (10^{-4} M) and *N*-*N'*-dicyclohexylcarbodiimide (10^{-5} M) inhibitors of $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity, blocked PMA-stimulated cell division, but not that due to serum. Three cell-cycle stages are sensitive to dbcAMP: early G_1 , G_1 -S transition, and the passage from post-S to mitosis. The membrane sites responsible for the critical functions may be clustered and physically dependent on each other for conformational allosteric changes associated with the regulation of cell division. Further, inhibition of any single function appears to be sufficient to block the entire process. (36 refs.)

77-6751 The Presence of Aryl Hydrocarbon Hydroxylase and Epoxide Hydrase in Rat Liver Nucleoli (Meeting Abstract). (Eng) Lafarge-Frayssinet, C. (Institut de Recherches Scientifiques sur le Cancer, B. P. N 8-94 800 Villejuif, France); Alexandrov, K.; Dansette, P. M.; Guerry, R.; Frayssinet, C. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 85; 1977. (no refs.)

77-6752 Genetic Differences in Induction of Cytosol Reduced-NAD(P):Menadione Oxidoreductase and Microsomal Aryl Hydrocarbon Hydroxylase in the Mouse.

(Eng) Kumaki, K. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD 20014); Jensen, N. M.; Shire, J. G.; Nebert, D. W. *J Biol Chem* 252(1): 157-165; 1977.

The stimulation of NADPH:menadione oxidoreductase activity in liver cytosol was highly correlated with the stimulation of hepatic microsomal benzo(a)pyrene aryl hydrocarbon hydroxylase (AHH) activity in 3-methylcholanthrene (3-MC)-, β -naphthoflavone-, phenobarbital-, or pregnenolone-16 α -carbonitrile-treated inbred C57BL/6N and DBA/2N mice and in eight other inbred strains treated with 3-MC. No oxidoreductase activity was detectable in mouse liver microsomes. Cytochrome and 2,6-dichlorophenolindophenol were equally good electron acceptors for the oxidoreductase. There was no preferential in vitro inhibition of induced vs control oxidoreductase activities by α -naphthoflavone or metyrapone. In 3-MC-treated F_1 and F_2 progeny and offspring from backcrosses between the F_1 and either C57BL/6N or DBA/2N parent, there was no strict correlation between induced or noninducible AHH and oxidoreductase activities. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin, at doses of 80 $\mu\text{g}/\text{kg}$, induced the oxidoreductase about threefold in C57BL/6N and $< 50\%$ in DBA/2N mice. The data are consistent with the hypothesis that two loci (*Ox-1* and *Ox-2*) regulate oxidoreductase induction by 3-MC, that one of the genes is linked to the *Ah* locus (with an estimated recombination frequently between 2% and 23%), and that the other gene is not linked to the *Ah* locus. These experimental data might be useful in the protein activator hypothesis of the Britten-Davidson model for gene regulation. (50 refs.)

77-6753 Characterization of Rat Lung Epoxide (Styrene Oxide) Hydrase with a Modified Radioactive Assay of Improved Sensitivity. (Eng) Seidegard, J. (Arrhenius Lab., Dept. Biochemistry, Univ. Stockholm, Fact, S-104 05 Stockholm, Sweden); DePierre, J. W.; Moron, M. S.; Johannessen, K. A.; Ernster, L. *Cancer Res* 37(4): 1075-1082; 1977.

An epoxide hydrase assay that used ^3H -styrene oxide as substrate was modified for use with rat lung microsomes. In Sprague-Dawley rat lungs, the enzyme had an apparent V_{max} of 0.5 nanomole of styrene glycol formed/min/mg microsomal protein; its apparent K_m was 0.11 to 0.25 nM. The pH optimum was 9.7. After subcellular fractionation of lung tissue, the distributions of epoxide hydrase resembled that of a marker for the endoplasmic reticulum (NADPH-cytochrome *c'* reductase); but it differed from that of markers for the nuclei, mitochondria, concentric lamellar organelles, lysosomes, Golgi membranes, plasma membrane, and soluble cytoplasm. The specific activity of epoxide hydrase was similar in rough and smooth lung microsomes. Treatment of rats with ip methylcholanthrene (3 injections of 20 mg/kg), phenobarbital (5 injections

of 80 mg/kg), or styrene oxide (5 injections of 40 mg/kg) did not induce lung microsomal epoxide hydase activity. 1,1,1-Trichloropropene 2,3-oxide was an uncompetitive inhibitor and cyclohexene oxide was a non-competitive inhibitor of this enzyme. Ethanol and butanol activated epoxide hydase at low concentrations and inhibited it at high concentrations. (61 refs.)

77-6754 Genetic Regulation of UDP-Glucuronosyltransferase Induction by Polycyclic Aromatic Compounds in Mice. Co-segregation with Aryl Hydrocarbon [Benzo(a)pyrene] Hydroxylase Induction. (Eng) Owens, I. S. (Developmental Pharmacology Branch, Natl. Inst. Child Health and Human Development, NIH, Bethesda, MD 20014). *J Biol Chem* 252(9): 2827-2833; 1977.

3-Methylcholanthrene (3-MC) induction of hepatic uridine diphosphate (UDP)-glucuronosyl-transferase was examined in various strains of mice to determine whether this activity is under genetic control. 3-MC induces the enzyme in C57BL/6N, A/J, PL/J, C3HeB/FeJ, and BALB/cJ mice, but not in DBA/2N, AU/SsJ, AKR/J, or RF/J inbred mice. Induction is max in C57BL/6N mice with 200 mg/kg 3-MC ip, but no induction occurs in DBA/2N mice with a dose of 400 mg/kg. The rise in activity lags 1 or more days behind inducible hydroxylase activity and peaks 5 days after 3-MC. In offspring from appropriate backcrosses and intercrosses between C57BL/6N and DBA/2N strains, the inducible trait is inherited as a codominant one. This expression differs from that of inducible hydroxylase activity, which is inherited almost exclusively as a single autosomal dominant trait. 2,3,7,8-Tetrachloro-dibenzo-p-dioxin (TCDD: 50 µg/kg ip) induced the transferase more than threefold in C57BL/6N mice and less than twofold in DBA/3N mice; hydroxylase was induced about eightfold in both strains. When two 40- mg/kg doses of 3-MC were administered 3 days after 25 µg/kg TCDD, there was no enhancement of the rise in inducible transferase activity seen in mice that received TCDD alone. These results indicate that the inducibility of transferase and hydroxylase activities may be regulated by the same genetic locus (*Ah*), most likely through a common cytosolic receptor, and that although hydroxylase can be induced in DBA/2N mice by TCDD prior to MC treatment, MC metabolites are incapable of inducing further transferase activity. (39 refs.)

77-6755 The Effects of Anti-inflammatory Agents on Skin Tumor Initiation and Aryl Hydrocarbon Hydroxylase. (Eng) Slaga, T. J. (Cancer and Toxicology Program, Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Viaje, A.; Bracken, W. *Res Commun Chem Pathol Pharmacol* 16(2): 337-350; 1977.

The effects of some nonsteroidal anti-inflammatory agents on 3-methylcholanthrene (3-MC) skin tumor initiation in the

mouse and on epidermal aryl hydrocarbon hydroxylase (AHH) activity were investigated. Oxyphenbutazone (OPB) inhibited 3-MC-induced tumor initiation, but it was less effective than the steroidal anti-inflammatory agent dexamethasone. OPB did not induce AHH activity in mouse epidermis but Indomethacin and Seclazone had a slight inducing effect. When these agents were added directly to the in vitro AHH assay, they did not inhibit AHH activity. There was a decreased epidermally mediated covalent binding of 3-MC to DNA in vitro when the epidermal homogenates were isolated from mice pretreated with either dexamethasone or OPB and 3-MC at 3 or 12 hr before killing. Both dexamethasone and OPB apparently inhibit the formation of some electrophilic intermediate(s) of MC as a result of an indirect effect on the epidermal mixed-function oxidase. (17 refs.)

77-6756 Interindividual and Intraindividual Variation in Aryl Hydrocarbon Hydroxylase in Monocytes from Monozygotic and Dizygotic Twins. (Eng) Okuda T. (Biology Branch, NCI, NIH, Bethesda, MD 20014); Vessel, E. S.; Plotkin, E.; Tarone, R.; Bast, R. C.; Gelboin, H. V. *Cancer Res* 37(11): 3904-3911; 1977.

Intra- and interindividual variations in the basal and benz(a)anthracene-induced levels of aryl hydrocarbon hydroxylase (AHH) were investigated in cultured monocytes from 10 sets of monozygotic and 17 sets of dizygotic normal adult twin volunteers. The values for basal levels and, therefore, for induction ratios were more variable than those of induced levels. The mean values for the induced levels ranged from 4.26 to 17.69. Intratwin differences in the induced levels were small within monozygotic and most dizygotic twins. However, several sets of dizygotic twins had much greater intratwin differences than the monozygotic twins. Genetic factors accounted for approx one-half to two-thirds of the total interindividual variation in AHH inducibility, the other one-half to one-third of the total variation being attributable to environmental factors. On repeated analysis of the same twin set, the magnitude of the difference within the twin set remained small, although the absolute values changed appreciably from one assay to the next. This suggests that the absolute induced values are influenced significantly by unidentified factors in the laboratory procedures that fluctuate from one monocyte assay to the next. These data also suggest that genetic factors play a large role in determining the induced AHH value. (40 refs.)

77-6757 Aryl Hydrocarbon Hydroxylase Activity in Pulmonary Macrophages and Lymphocytes from Lung Cancer and Noncancer Patients. (Eng) McLemore, T. L. (Dept. Medicine, Infectious Diseases Section, Baylor Coll. Medicine, Texas Medical Center, Houston, TX 77030); Martin, R. R.; Busbee, D. L.; Richie, R. C.; Springer, R. R.; Toppell, K. L.; Cantrell, E. T. *Cancer Res* 37(4): 1175-1181; 1977.

Aryl hydrocarbon hydroxylase (AHH) activity was measured in pulmonary alveolar macrophages and peripheral blood lymphocytes from 47 patients with primary lung cancer and 66 patients bronchoscoped for other indications. Nonsmokers without cancer had lower macrophage AHH activity [16 milliunits (mU)/ 10^6 cells] than nonsmokers with lung cancer (24 mU/ 10^6 cells). Although macrophage enzyme values were consistently higher in smokers than in nonsmokers, smokers with lung cancer and smokers without cancer had similar levels (77 and 95 mU/ 10^6 cells, respectively). AHH induction in lymphocytes from nonsmokers was significantly lower for the cancer patients than those without cancer; however, induction was similar in lymphocytes from smokers whether or not they had lung cancer. In patients without lung cancer, macrophage enzyme levels correlated with induced lymphocyte levels. Enzyme values for cells from smokers with lung cancer did not correlate, and an inverse relationship was noted with cells from nonsmoking cancer patients. The absence of a correlation between macrophage and lymphocyte AHH activity may be of diagnostic value in the early detection of lung cancer. (39 refs.)

77-6758 Effect of Cigar Smoking on Carboxyhaemoglobin and Plasma Nicotine Concentrations in Primary Pipe and Cigar Smokers and Ex-cigarette Smokers. (Eng) Turner, J. A. (Dept. Medicine, Middlesex Hosp., London W1, England); Sillett, R. W.; McNicol, M. W. *Br Med J* 2(6099): 1387-1389; 1977.

The degree of inhalation of primary pipe and cigar smokers was compared with that of ex-cigarette smokers after each smoked a large cigar. Blood carboxyhemoglobin was used as a measure of inhalation, plasma nicotine as a measure of nicotine absorption. The results indicated that the ex-cigarette smokers had inhaled and had absorbed significant amounts of nicotine, whereas the cigar and pipe smokers had not. Thus, nicotine absorption is mainly from the lungs, and not the buccal mucosa. Since ex-cigarette smokers do not lose their habit of inhaling, switching from cigarettes to cigars or pipes will have little value on their health. (16 refs.)

77-6759 Transplacental Effects of Nitrosamines in Syrian Hamsters. II. Nitrosopiperidine. (Eng) Althoff, J. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NB 68105); Grandjean, C.; Marsh, S.; Pour, P.; Takahashi, M. *Z Krebsforsch* 90(1): 71-77; 1977.

Pregnant Syrian hamsters were injected sc with 100 mg/kg nitrosopiperidine (NP) or 50 mg/kg nitrosohexamethyleneimine (N6MI). Although NP disappeared from the placenta, fetus, and amniotic fluid by 8 hr, maternal blood concentrations remained high at this time. Only traces of N6MI were present after 2 hr in the same tissues. The long-term transplacental effect of a single dose (100 mg/kg) of NP was weak, as demonstrated by a low respiratory tract tumor incidence

(4% in the F_1 generation versus 54% in the parent generation). Some digestive tract tumors in F_1 animals were not found in their mothers and were not common in controls. These tumors represented a borderline transplacental effect. Tumors of other sites (ie, the urogenital and genital tracts, reticuloendothelial system, endocrine organs) corresponded in incidence to the overall fluctuations observed in the hamster colony. (26 refs.)

77-6760 A Method for Detecting Carcinogenic Organic Chemicals Using Mammalian Cells in Culture. (Eng) Styles, J. A. (Imperial Chemical Industries Limited, Central Toxicology Lab., Alderley Park, Macclesfield, Cheshire, England). *Br J Cancer* 36(5): 558-563; 1977.

A method for testing organic chemicals for their carcinogenic potential is described. Baby hamster kidney cells (BHK-21/Cl 13) were exposed to different doses of a test compound (nitrosofolic acid, diphenylnitrosamine) in liquid tissue culture medium containing rat liver post-mitochondrial supernatant and cofactors (S-9 mix) to aid metabolism, but without serum. Survival of cells following exposure to the compound was assessed by cloning in liquid growth medium. Transformation was assessed by colony growth in semi-solid agar. The dose-response curve for survival was used to determine the LC_{50} (50% lethal concentration) of the compound. A dose-response curve for transformation was constructed, and a five fold increase in transformation frequency at the LC_{50} was regarded as a positive result. For application of the method to gases, cells grown in monolayers and overlaid with serum-free medium and S-9 mix were exposed to vinyl chloride gas mixed with air. After exposure, the treated cells were trypsinized, resuspended in growth medium, and survival and transformation assays performed. Increases in transformation frequency were seen with nitrosofolic acid and vinyl chloride gas. In a study using 120 compounds, the methods described were > 90% accurate in distinguishing between carcinogens and noncarcinogens. (19 refs.)

77-6761 Mutagenicity of Five Cyclic N-Nitrosamines: Assay with *Salmonella typhimurium*. (Eng) Stoltz, D. R. (Food Res. Labs., Health Protection Branch, Tunney's Pasture, Ottawa K1A 0L2, Canada); Sen, N. P. *J Natl Cancer Inst* 58(2): 393-394; 1977.

The mutagenicity of five cyclic N-nitrosamines was tested in *Salmonella typhimurium* TA1535 with and without microsomal activation. Doses ranged up to 500 μ g/plate for each compound. Spot tests were also conducted in which a few milligrams of the agents were put directly on the agar surface. Nitrosopiperidine, nitrosopyrrolidine, and nitroso-3-pyrrolidinol were mutagenic, but nitrosoproline and nitrosohydroxyproline were inactive in both the plate incorporation assays and spot tests. In the absence of liver microsomes, however, only nitroso-3-pyrrolidinol was mutagenic, indicating

a role of hydroxylation in the metabolic activation of nitrosopyrrolidine to an ultimate carcinogen. However, this does not exclude the possibility that other metabolic products could be more active proximate carcinogens. (15 refs.)

- 77-6762 Induction of Epithelial Neoplasms by Local Application of N-Nitrosobis(2-hydroxypropyl)amine and N-Nitrosobis(2-acetoxypentyl)amine.** (Eng.) Pour, P. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center 42nd and Dewey Ave., Omaha, NB 68105); Althoff, J.; Nagel, D. *Cancer Lett* 3(3-4): 109-113; 1977.

The local tumorigenic potency of N-nitrosobis(2-hydroxypropyl)amine (BHP) and N-nitrosobis(2-acetoxypentyl)amine (BAP) was demonstrated by topical application to the cheek pouch, lip, and vaginal epithelium of 8-wk-old female Syrian golden hamsters. A 10% solution of BHP or a 14% solution of BAP were applied weekly for life (10 hamsters/group). The estimated max weekly dose was 0.3 ml/animal (30 mg BHP and 42 mg BAP). After about 20 wk from the start of treatment, small excrescences along the upper and lower lips were observed in 19 hamsters. The animals survived for an av of 33 (BHP) and 41 (BAP) wk. Tumor type and incidence in the BHP- and BAP-treated animals, respectively, were: trichoepitheliomas of the lip, 80% and 90%; cheek pouch papillomas, 10% and 0%; vaginal papillomas, 80% and 70%. Lesions in other tissues (polyps of the uterine cervix, perineal epidermal hyperplasia, transitional cell papilloma in the external urethral orifice, and carcinoma in situ at the anal-rectal border) were due to a local effect, since equivalent alterations were not found after sc administration of BHP or BAP. The results possibly indicate that lip or vaginal epithelium can metabolically activate these compounds or that the particular chemical structures of BHP and BAP endow them with local activity. (7 refs.)

- 77-6763 Kinetics of Nitrosamine Formation in the Presence of Micelle-forming Surfactants.** (Eng) Okun, J. D. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA 02139); Archer, M. C. *J Natl Cancer Inst* 58(2): 409-411; 1977.

The possible catalytic effect of micelles, spherical molecular aggregates of surfactants in aqueous media, on the formation of nitrosamines from nitrous acid and secondary amines was investigated. Below 0.04 M of the surfactant decyltrimethylammonium bromide (DTAB), no significant changes in the nitrosation of dihexylamine were observed. At 0.4 M, however, the initial rate was enhanced 800 times. The critical micelle concentration was calculated to be 6.3×10^{-2} M, a value that corresponded to the concentration of DTAB needed to increase nitrosation. Amine structure also influenced the catalytic effect of micelles on nitrosation. As the alkyl

chain length of the secondary amine increased, so did the magnitude of the catalytic effect. The effects of two other surfactants on catalysis of dihexylamine formation were studied. Nitrosation was enhanced 100 times with 0.4% of the nonionic detergent Triton X-100 (alkylphenoxypolyethoxyethanol) and 220 times with 0.8% phosphatidylcholine, a phospholipid lecithin. The enhancement by lecithin is a particularly significant finding because of the abundance of lecithin in biologic systems, including food. Lecithin is also used commercially as a lubricant and antisticking agent for cookwear. (15 refs.)

- 77-6764 Metabolism of N-Nitrosohexamethyleneimine To Give 1,6-Hexanediol Bound to Rat Liver Nucleic Acids.** (Eng) Ross, A. E. (Eppley Inst. Res. Cancer Univ. Nebraska Medical Center, 42nd St. and Dewey Ave., Omaha, NB 68105); Mirvish, S. S. *J Natl Cancer Inst* 58(3): 651-655; 1977.

Male Wistar rats were given the hepatocarcinogen N-nitrosohexamethyleneimine (NHX: 60 mg/kg by gavage) labeled with ^3H or ^{14}C and killed 16 hr later. The liver RNA and DNA were isolated and hydrolyzed with 1 M HCl at 100°C. Chromatography of the ^3H -labeled RNA hydrolysate on a cation exchange resin (NH_4^+ form) with water elution separated five radioactive peaks, with peak E containing 27% of the bound ^3H . There were no radioactive peaks in the 7-substituted guanine region. Hydrolysis of the ^3H -labeled DNA gave a similar profile, but E contained only 5% of the ^3H . The major component of E was identified as 1,6-hexanediol by its behavior and/or that of its benzoate derivative on cation exchange, anion exchange, thin-layer and gas-liquid chromatography and by recrystallization of a mixture of the E and diol benzoates to constant specific radioactivity. (25 refs.)

- 77-6765 Reduction of N-Nitrosodiethylamine Carcinogenesis in Rats by Lipotrope or Amino Acid Supplementation of a Marginally Deficient Diet.** (Eng) Rogers, A. E. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA 02139). *Cancer Res* 37(1): 194-199; 1977.

When added to a diet marginally deficient in lipotropes (choline, methionine, folic acid), amino acids, and niacin, and high in fat, N-nitrosodiethylamine (DENA, 40 ppm for 12 wk) markedly increased the incidence of hepatocarcinomas in Sprague-Dawley rats. Supplementation of marginally deficient diet with amino acids or lipotropes significantly decreased tumor induction by DENA. Niacin supplementation decreased tumor incidence only slightly; the addition of beef fat to an adequate diet had no effect. Rats fed the amino acid- or lipotrope-supplemented diets had a higher incidence of hepatic hemangioendothelial sarcomas than rats fed the deficient diet or rats fed the adequate control diet. Methionine was contained in both the amino acid and the lipotrope sup-

plement, and it probably was responsible for reducing hepatocarcinoma incidence. Other studies have also found that methionine has an anticarcinogenic effect and that it blocks the DENA-induced depletion of hepatic folate stores. Interactions between carcinogens, S-adenosylmethionine, and folate may be significant in hepatic or other tissue carcinogenesis. A depression of hepatic microsomal oxidases in rats fed any of the high-fat diets was correlated with tumor incidence. (29 refs.)

77-6766 Variations of Liver Cell Control During Diethylnitrosamine Carcinogenesis. (Eng) Barba-son, H. (Laboratoire d'Anatomie Pathologique, Institut de Pathologie Universite de Liege au Sart Tilman, 4000 Liege, Belgium); Fridman-Manduzio, A.; Lelievre, P.; Betz, E. H. *Eur J Cancer* 13(1): 13-18; 1977.

Variations in liver cell control were studied during the preneoplastic state (up to 60 days) of carcinogenesis induced in male Wistar rats by 80 mg/liter diethylnitrosamine (DENA) in the drinking water. Some of the DENA-treated rats were subjected to partial hepatectomy. During the first 2 wk, DENA produced a transient increase in the mitotic index; after partial hepatectomy, the mitotic response was nearly normal. Cell division during this time approximated a normal circadian rhythm. After 30 days of treatment, the mitotic index decreased significantly, the response to partial hepatectomy was reduced, and the circadian rhythm of cell division was lost. In addition, glycogen-retaining areas developed in the liver, and there was no difference between the response of these areas and that of the adjacent parenchyma. When drug administration was interrupted on day 50 and hepatectomy was performed on day 60, the results were the same as those after a DENA feeding period of 60 days. When normal hepatectomized rats were treated with liver extracts from normal rats, the ³H-thymidine DNA label and the mitotic response induced by partial hepatectomy were inhibited. A similar extract from liver tissue taken 24 hr after hepatectomy had no inhibitory effect. Extracts from liver of rats treated for 30 to 60 days with DENA also had no inhibitory effect. Apparently, mechanisms controlling liver cell homeostasis function normally for 2 wk, but at later dates, these mechanisms are significantly altered. (20 refs.)

77-6767 Inhibition of Diethylnitrosamine-induced Strand Breaks in Liver DNA by Disulfiram. (Eng) Hadjiolov, D. (Institut für Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany); Frank, N.; Schmahl, D. *Z Krebsforsch* 90(1): 107-109; 1977.

When administered 1 hr before diethylnitrosamine (DEN, 100 mg/kg, ip), a single dose of disulfiram (DSF, 500 mg/kg) delayed for at least 4 hr the appearance of carcinogen-induced strand breaks in liver DNA of Wistar rats. Although strand breaks were observed 24 hr after DEN administration,

it is possible that continuous treatment with DSF might protect against damage to genetic material. (11 refs.)

77-6768 The Role of Nicotinamide and of Certain Other Modifying Factors in Diethylnitrosamine Carcinogenesis: Fusaria Mycotoxins and 'Spontaneous' Tumors in Animals and Man. (Eng) Schoental, R. (Dept. Pathology, Royal Veterinary Coll., Royal Coll. St., London NW1 OTU, England). *Cancer [Suppl]* 40(4): 1835-1840; 1977.

Pretreatment of white Wistar rats with nicotinamide (350-500 mg/kg, ip), which has been shown to increase the incidence of pancreatic islet-cell tumors after streptozotocin and heliotrine, appeared to promote the development of kidney neoplasms in animals given several doses of diethylnitrosamine (100 mg/kg, ip or by stomach tube). Nicotinamide, a B vitamin and a constituent of NAD coenzymes, will prevent the depletion of NAD coenzymes by alkylating agents. It may offer some protection against the acute effects of hepatocarcinogens but not against tumor induction, although it may change the localization of the latter. The possible mechanisms involved in the action of nicotinamide and certain other modifying agents are discussed. Pituitary, mammary, and certain other tumors that sometimes occur in control and experimental animals may be due to the presence of estrogenic and/or toxic secondary metabolites of the field fungi *Fusaria* in laboratory animal diets. Mycotoxins, such as zearalenone and the trichothecenes, are also likely to contaminate human foods; this could explain why multiple tumors in man occur mainly in the sex-organs and in the digestive tract. (48 refs.)

77-6769 Tumor Frequency and Characteristics after a Single Dose of Dimethylnitrosamine or Diethylnitrosamine in Partially Hepatectomized Rats. (Eng) Fridman-Manduzio, A. (Laboratoire d'Anatomie Pathologique, Universite de Liege, 1, rue des Bonnes Villes, B-4020, Liege, Belgium); Gol-Winkler, R.; Betz, E. H.; Goutier, R. *Z Krebsforsch* 90(1): 13-24; 1977.

Wistar rats in groups of 75 animals each were inoculated ip with a single dose of 9 mg/kg dimethylnitrosamine (DMNA) or 120 mg/kg diethylnitrosamine (DENA) at 28 hr after partial hepatectomy. Control nonhepatectomized rats received single injections of DMNA or DENA (20 and 200 mg/kg, respectively), at doses equitoxic to those administered to partially hepatectomized rats. Another control group of partially hepatectomized rats was injected with saline. Tumor frequencies in the nitrosamine-treated rats were as follows: (1) for DMNA: 13% in liver, 13% in kidney, 4% in lung, 4% at surgical scar, 9% in hematopoietic tissue, and 13% in other organs; (2) for DENA: 11% in liver, 27% in kidney, 2% at surgical scar, 2% in hematopoietic tissue, and 11% in other organs. The histological characteristics of these tumors are described. No significant difference existed in the overall tumor incidence induced by DMNA and DENA, but

the difference between liver and kidney tumors induced by DENA was significant. The difference between DMNA- and DENA-induced kidney tumors was less significant. Death from tumors occurred at an earlier time after DENA than after DMNA, and liver tumors appeared at a significantly earlier time after DENA than after DMNA. The longer half-life of DENA may be responsible for the shorter tumor induction time observed for this drug compared with DMNA. However, liver tumor induction seems to be independent of half-life but strongly determined by the fact that the proximate carcinogen reaches the hepatic cells during the DNA synthesis phase. (42 refs.)

- 77-6770 Microsome-mediated Mutagenesis in V79 Chinese Hamster Cells by Various Nitrosamines.** (Eng) Kuroki, T. (International Agency Res. Cancer, Unit Chemical Carcinogenesis, 150 Cours Albert Thomas, 69008 Lyon, France); Drevon, C.; Montesano, R. *Cancer Res* 37(4): 1044-1050; 1977.

The mutagenicity of various nitrosamines, determined by resistance to 20 $\mu\text{g/ml}$ 8-azaguanine, was studied in V79 Chinese hamster cells treated in the presence of a postmitochondrial fraction (S15) from rat liver and NADH generating system. N-Nitrosodimethylamine (DMN) was mutagenic and cytotoxic only in the presence of the S15 fraction and cofactors. Pretreatment of rats with phenobarbital increased the mutagenic effect of 10-50 mM DMN twofold over that with tissues from untreated rats. Aminoacetonitrile pretreatment reduced the mutagenic effect, and methylcholanthrene increased its frequency, but only with high (50 mM) DMN concentrations. With the exception of N-nitrosomethylphenylamine, all carcinogenic nitrosamines (DMN, N-nitrosodiethylamine, N-nitrosodi-n-propylamine, N-nitrosodi-n-butylamine, N-nitrosodi-n-pentylamine, N-nitrosomethyl-n-propylamine, N-nitrosomorpholine, N-nitrosopyrrolidine, N-nitroso-N'-methyipiperazine, and N-nitrosomethylphenylamine) were mutagenic to the V79 Chinese hamster cells in the presence of the S15 fraction from phenobarbital-treated rats and cofactors. Neither N-nitrosodiphenylamine nor N-nitrosomethyl-tert-butylamine had a mutagenic effect. These findings show that chemical carcinogens can be tested for mutagenicity in cultured mammalian cells in the presence of a metabolic activation system. The carcinogenicity and mutagenicity of these compounds in other test systems are discussed. (36 refs.)

- 77-6771 Alkylation of Rat Liver DNA by Dimethylnitrosamine: Effect of Dosage on O⁶-Methylguanine Levels.** (Eng) Pegg, A. E. (Dept. Physiology and Specialized Cancer Res. Center, Milton S. Hershey Medical Center, Pennsylvania State Univ., 500 Univ. Drive, Hershey, PA 17033). *J Natl Cancer Inst* 58(3): 681-687; 1977.

The alkylation of liver DNA was studied in Sprague-Dawley rats treated with dimethylnitrosamine (DMN: 0.25-20 mg/kg

ip). The amounts of O⁶-methylguanine (MeG) and methylguanine in liver DNA were determined at 4 and 24 hr after DMN treatment. There was a linear relationship between 7-methylguanine levels and nitrosamine dose at both of these times. In contrast, the MeG levels were not directly proportional to dose; they were less than expected, particularly at doses < 2.5 mg/kg. This discrepancy was significant at 4 hr and even more marked at 24 hr. Only doses > 2.5 mg/kg at the 4-hr time point gave rise to a 0.11 ratio of alkylation of guanine at the O⁶-position to that at the 7-position. This was the expected ratio for the initial interaction of the alkylating species derived from DMN with DNA. Evidence was obtained to support the hypothesis that these results were due to an enzymatic removal of MeG from liver DNA, which occurred much more efficiently at low initial alkylation levels. Repeated daily injections of DMN up to 11 days also gave rise to MeG levels that were not proportional to dose but that were relatively greater at high dose levels. The significance of these findings in the induction of liver cancer by feeding or repeated injection of DMN is discussed. (44 refs.)

- 77-6772 Induction of 6-Thioguanine-resistant Mutants in V79 Chinese Hamster Cells by Mouse-Liver Microsome-activated Dimethylnitrosamine.** (Eng) Abbondandolo, A. (Laboratorio di Mutagenesi e Differenziamento, CNR, Pisa, Italy); Bonatti, S.; Corti, G.; Fiorio, R.; Loprieno, N.; Mazzaccaro, A. *Mutat Res* 46(5): 365-373; 1977.

A study of the induction of 6-thioguanine-resistant mutants in V79 Chinese hamster cells following dimethylnitrosamine activation of crude and purified mouse liver microsomal preparations revealed a linear increase in mutant frequency. The more purified microsomes had a reduced ability to activate the mutagen; this was probably a result of the methodology used. (30 refs.)

- 77-6773 Morphologic Character of Transforming Renal Cell Cultures Derived from Wistar Rats Given Dimethylnitrosamine.** (Eng) Hard, G. C. (Dept. Pathology, Univ. Melbourne Medical Center, Grattan St., Parkville, Victoria, Australia); Borland, R. *J Natl Cancer Inst* 58(5): 1377-1382; 1977.

The morphologic character of serial subcultures of kidney cells from Wistar rats treated several hours to 1 wk previously with a carcinogenic dose of dimethylnitrosamine (DMN: 80 mg/kg, ip, following protein deprivation) was compared with that of cultured cells from normal rats. Apart from early signs of toxicity, cells from DMN-treated rats resembled those from untreated rats for the first four passages. Most control cells underwent senescence by subculture 4, but the test cells survived to express morphologic transformation (usually at subculture 5) as dense macroscopic colonies of piled-up cells. In 18/20 test cultures, the cells that persisted in continuous culture after morphologic transformation were

exclusively mesenchymal; they resembled mesenchymal tumor cells in continuous culture. The remaining two test cultures contained abnormal epithelial cells in addition to transformed mesenchymal cells. These results are compatible with the high incidence of mesenchymal tumors and the lower incidence of cortical tumors induced in vivo by the same DMN dose schedule. (9 refs.)

77-6774 Studies on the In Vitro Metabolism of Dimethylnitrosamine by Rat Liver. (Eng) Lake, B. G. (British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey, SM5 4DS, England); Phillips, J. C.; Heading, C. E.; Gangolli, S. D. *Toxicology* 5(3): 297-309; 1977.

Incubation of hepatic subcellular fractions from male Wistar albino rats with 5 millim dimethylnitrosamine (DMN) showed that the DMN demethylase activity was contained almost entirely in the postmitochondrial fraction and that the microsomes contained 50% of this activity. The enzyme kinetics of this fraction revealed three distinct kinetic plots, indicating that enzymatic degradation of DMN to formaldehyde is a multistep process. In contrast to the 60% loss in stability of cytochrome P-450 after 17 days of storage, DMN demethylase showed only a 15% loss. In spectral interaction studies, the addition of 0.6 millim DMN to untreated, phenobarbitone-treated, and phospholipid-depleted microsomes produced unique spectral shifts. At 16.4 millim, DMN non-competitively inhibited the spectral interactions of benzphetamine and biphenyl (Type I substrates), but had little effect on the Type II spectral interaction of aniline. In contrast to the four oxidative enzymes studied, DMN inhibited the activity of 4-nitrobenzoic acid anaerobic reductase. The results indicate that rat hepatic DMN demethylase differs from several microsomal mixed function oxidases dependent on cytochrome P-450 and suggest that DMN may be degraded by a metabolic pathway involving N-oxidation. (51 refs.)

77-6775 Effects of Pyrazole and 3-Amino-1,2,4-triazole on the Metabolism and Toxicity of Dimethylnitrosamine in the Rat. (Eng) Phillips, J. C. (British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton Beeches, Surrey, SM5 4DS, England); Lake, B. G.; Gangolli, S. D.; Grasso, P.; Lloyd, A. G. *J Natl Cancer Inst* 58(3): 629-633; 1977.

Pretreatment of Porton-Wistar rats with pyrazole (40 or 200 mg/kg, ip) or 3-amino-1,2,4-triazole (3-AT: 200 or 1,000 mg/kg, ip) markedly inhibited the metabolism of dimethylnitrosamine (DMN: 5 mg/kg) in terms of ^{14}C -CO excretion and blood DMN levels. Additionally, 4-methylpyrazole (10 mg/g), disulfiram (100 mg/kg), methanol (1 g/kg), and ethanol (10 g/kg) inhibited DNA metabolism in the whole animal. In parallel experiments with ^{14}C -aminopyrine (15.6 mg/kg), no substantial inhibitory effect was seen after pyrazole, 3-AT, or disulfiram pretreatment. Toxicity studies showed that

pyrazole significantly increased the LD50 of DMN and provided substantial protection against its hepatotoxicity, in that centrilobular necrosis was not observed at doses up to 25 mg/kg and early histochemical changes indicative of liver damage were not seen at 15 mg/kg DMN. 3-AT pretreatment did not affect the LD50 of DMN or inhibit its hepatotoxicity. Furthermore, 3-AT was significantly less effective than pyrazole in delaying the incorporation of radioactivity from ^{14}C -DMN into hepatic subcellular organelles. (27 refs.)

77-6776 Transplacental Effects of Nitrosamines in Syrian Hamsters. III. Dimethyl- and Dipropylnitrosamine. (Eng) Althoff, J. (Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NB 68105); Pour, P.; Grandjean, C.; Marsh, S. *Z Krebsforsch* 90(1): 79-86; 1977.

Pregnant Syrian hamsters were injected sc with 12.5 mg/kg dimethylnitrosamine (DMN) or with 100 mg/kg diethylnitrosamine, dipropylnitrosamine (DPN), or dibutylnitrosamine (DBN). Quantitatively measurable amounts of the compounds reached fetal tissue. The compounds were present for at least 2 hr in maternal blood, placenta, fetus, and amniotic fluid; DBN was still measurable after 6 hr. Only a weak or borderline transplacental effect was seen when incidences and latencies of neoplasms in the respiratory and digestive tracts of the F_1 generation were compared with those of the parent generation after exposure to a single dose of DMN or DPN. However, some tumors with relatively high incidence rates in the young were rare in the mothers or in the hamster colony in general. (19 refs.)

77-6777 Mechanism of Alkylation by N-Nitroso Compounds: Detection of Rearranged Alcohol in the Microsomal Metabolism of N-Nitrosodi-n-propylamine and Base-catalyzed Decomposition of N-n-Propyl-N-nitrosourea. (Eng.) Park, K. K. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA 02139); Wishnok, J. S.; Archer, M. C. *Chem Biol Interact* 18(3): 349-354; 1977.

The metabolism of N-nitrosodi-n-propylamine (NDPA) in isolated male albino Sprague-Dawley rat liver microsomal fractions and the base-catalyzed decomposition of N-n-propyl-N-nitrosourea (PNU) were studied to investigate the alkylation of these carcinogens. NDPA was added at a concentration of 40 μL , and the reaction was allowed to proceed for 15 min; PNU was prepared from n-propylurea. The proportion of the n-propanol and isopropanol products of the in vitro and chemical reactions were 83% and 17%, respectively, for the in vitro reaction and 61% and 39%, respectively, for the chemical reaction. These findings indicate that formation of propanol by the microsomal metabolism of the amine takes place through a carbocation. Experiments are underway to determine whether administration of the chemicals to animals results in the formation of isopropylated and n-propylated DNA bases. (22 refs.)

- 77-6778 **Transplacental Carcinogenesis and Chemical Determination of 1-Butyl-1-nitrosourea in Stomach Content after Simultaneous Oral Administration of 1-Butylurea and Sodium Nitrite to ACI/N Rats.** (Eng) Makawa, A. (Dept. Chemical Pathology, Kamiyoga 1-18-1, Setagaya-ku, Tokyo 158, Japan); Ishiwata, H.; Odashima, S. *Gann* 68(1): 81-87; 1977.

The transplacental carcinogenic effect of 100 mg/kg 1-butylurea and 50 mg/kg sodium nitrite administered by stomach tube daily from days 13 to 21 of pregnancy was investigated in ACI/N rats. Tumors occurred in 29/36 weaned offspring of these rats, and they were located in the nervous system (23), testis (4), pituitary gland (2), urinary bladder (3), and colon (1). Tumor incidence in the offspring of mothers receiving 1-butylurea only was 7/23, and these were located in the testis (4), uterus (2), and pituitary (1). Most of the nervous system tumors were localized in the hemispheres and spinal nerves, followed by the pons and medulla, spinal cord, and trigeminal nerve. Histologically, the nervous system tumors were neurinomas, oligodendrogliomas, mixed gliomas, astrocytomas or astroblastomas, and ependymomas. The amount of 1-butyl-1-nitrosourea (BNU) formed in the stomach of rats receiving both compounds was 25 ppm at 30 min and 23 ppm at 60 min, corresponding to 48.3 and 29.2 $\mu\text{g}/\text{rat}$, respectively. No BNU was detected when either substance was administered alone. (15 refs.)

- 77-6779 **Activation of the Renal Cortical and Hepatic Guanylate Cyclase-Guanosine 3',5'-Monophosphate Systems by Nitrosoureas. Divalent Cation Requirements and Relationship to Thiol Reactivity.** (Eng) Derubertis, F. R. (Dept. Medicine, Veterans Admin. Hosp., Pittsburgh, PA 15240); Craven, P. A. *Biochim Biophys Acta* 499(3): 337-351; 1977.

The action of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), streptozotocin, and N-methylnitrosourea (MNU) on the cyclic guanosine 3',5'-monophosphate (cGMP) content of male Sprague-Dawley rat renal cortex and liver was compared with that of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). The soluble enzyme activity of the renal cortex increased 32-fold in response to BCNU, 35-fold with streptozotocin, 35-fold with MNU, and 43-fold with MNNG. The respective figures for hepatic guanylate cyclase (GC) were 33-, 55-, 48-, and 64-fold. Lower concentrations of all the nitrosoureas were required for max stimulation of soluble renal cortical activity compared with soluble hepatic enzyme activity. With the particulate fractions of renal cortex and liver, the max increases were only two- to fourfold over the basal levels. The different concentrations of each agent required for max stimulation in the soluble and particulate fractions of each tissue are given. BCNU, MNU, and MNNG increased cGMP in the presence or absence of extracellular Ca^{2+} . Although basal renal cortex soluble GC activity was highly Mn^{2+} -dependent, the nitrosourea reactions were expressed with either Mn^{2+}

or Mg^{2+} as the only divalent cation; this was not observed with Ca^{2+} . With max stimulatory concentrations of streptozotocin or BCNU, Mg^{2+} or Mn^{2+} in high concentrations increased soluble GC levels. Preincubation of the supernatant fractions and the nitrosourea with dithiothreitol inhibited the increase in renal cortical GC activity; glutathione and cysteine were less inhibitory. A direct chemical interaction was probably responsible for the inhibition and was possibly related to thiol reactivity. Incubation of renal cortical supernatant fractions with N-ethylmaleimide or maleimide suppressed streptozotocin- or BCNU-mediated GC activity, possibly by preventing SH to SS transformation. (39 refs.)

- 77-6780 **Development of Peripheral Nervous System Tumors in Rabbits and Rats with Disturbed Ovarian Function.** (Rus) Beniashvili, D. Sh. (Scientific Res. Inst. Oncology, Ministry Health Georgian SSR, USSR, *Soobshch Akad Nauk Gruz SSR* 85(3): 729-732; 1977.

The effects of castration and estrogen treatment (sc Synestrol or dienestrol, implants, 60 mg/kg/mo) on the neurogenic tumor-inducing effect of methylnitrosourea (NMU) (10 mg/kg/wk, iv) were studied in random-bred female albino rats aged 2 mo and female rabbits aged 4-5 mo. Group 1 (70 rats and 20 rabbits) was castrated 15 days before the beginning of NMU treatment (day 1), Group 2 (70 rats and 20 rabbits) received Synestrol starting on day 3, and Group 3 (70 rats and 20 rabbits) received only NMU. The animals were observed for up to 3 yr. The incidences of peripheral nervous system tumors were 7/70 in rats and 1/20 in rabbits in Group 1, 19/70 in rats and 6/20 in rabbits in Group 2, and 15/70 in rats and 3/20 in rabbits in Group 3. The average latency times were 404.4 days for rats and 786 days for rabbits in Group 1, 180.3 days for rats and 456.9 days for rabbits in Group 2, and 323.4 days for rats and 720.4 days for rabbits in Group 3. Fourteen of the tumors were localized to the sciatic nerve. Ten tumors were malignant (9 neurogenic sarcomas, 1 sympatheticoblastoma); 41 were benign. The incidence of malignant tumors was highest in Group 2. The benign tumors included 24 fascicular neurinomas and 17 reticular neurinomas. The findings indicate the influence of ovarian hormone balance on the development of NMU-induced peripheral nervous system tumors. Tumor incidence was highest and the latency period shortest in estrogen-treated animals, but castration reduced the incidence and prolonged the latency period of the tumors. (8 refs.)

- 77-6781 **Activation of Guanylate Cyclase by Streptozotocin and 1-Methyl-1-nitrosourea.** (Eng) Vesely, D. L. (Div. Endocrinology and Metabolism, Dept. Medicine, Univ. Miami Sch. Medicine, Miami, FL 33152); Rovere, L. E.; Levey, G. S. *Cancer Res* 37(1): 28-31; 1977.

Streptozotocin, a compound that induces a variety of tumors in rats, and 1-methyl-1-nitrosourea, a component of strep-

tozotocin and a known carcinogen, are shown to stimulate guanylate cyclase, the enzyme that catalyzes the production of guanosine 3',5'-monophosphate. At a max concentration of 3 mg/ml, the two agents markedly stimulated guanylate cyclase activity in vitro in the liver, kidney, cerebellum, cerebrum, heart, brain stem, lung, and pancreas of Sprague-Dawley rats. Streptozotocin increased the enzyme activity ten- to thirtyfold in all these tissues except for the pancreas, which had a twofold stimulation. (29 refs.)

77-6782 Carbamoylation of DNA Bases Using N-Methyl-N-nitrosourea. (Rus) Serebrianyi, A.

M. (Inst. Chemical Physics, Acad. Sciences USSR, Moscow, USSR); Randalu, K. Kh. *Bioorg Khim* 3(5): 633-638; 1977.

The reaction of deoxycytidine with N-methyl-N-nitrosourea was studied under laboratory conditions. The deoxycytidine carbamoylation products isolated were identified as N⁴-carbamoyldeoxycytidine and 3-methyl-N⁴-carbamoyldeoxycytidine. These carbamoylation products, along with 3-methyluracil, a hydrolysis product, are unable to form Watson-Crick pairs. Therefore, the formation of these compounds in the DNA chain gives rise to sections with an altered secondary structure. These changes can lead to errors in template synthesis after replication. (19 refs.)

77-6783 Epithelial-Stromal Interactions in Normal and Chemical Carcinogen-treated Adult Bladder.

(Eng) Hodges, G. M. (Dept. Cellular Pathology, Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Hicks, R. M.; Spacey, G. D. *Cancer Res* 37(10): 3720-3730; 1977.

Cell membrane changes on the luminal aspect of the urothelium in vivo and in long-term organ cultures (100 days) of normal and N-methyl-N-nitrosourea (MNU)-treated rat bladders were studied by electron microscopy. The changes were also assessed in homotypic and heterotypic recombinations of the isolated epithelial and stromal components from normal and MNU-treated bladders. The maturation of normal uroepithelium in vivo was demonstrated on the basis of individual globular surface processes, their chainlike arrangement, and their amalgamation to form an angular membrane. In vitro, this sequence was reproduced only when the epithelium was in association with homotypic stroma. The absence of stroma led to atypical epithelial cell differentiation, with numerous irregular microvilli of varying size and orientation patterning the cell surface; this implies epithelial dependence on the stroma for normal cytodifferentiation. In MNU-induced benign and preneoplastic urothelial hyperplasia, short, swollen microvilli covered the luminal surface. Surface differentiation of the preneoplastic epithelium to overt neoplasia and tumor formation was associated with the appearance of increasingly complex and bizarre pleomorphic microvilli. Pleomorphic microvilli production was not reversed when neoplastic

epithelium was placed in heterotypic combination with normal bladder stroma, suggesting epithelial independence of stromal influence. By contrast, abnormal pleomorphic microvilli developed on the surface of normal urothelium associated with stroma from MNU-treated bladder; this implies a stromal effect on the epithelium and suggests that MNU may elicit new epithelial behavior by deranging stromal function. (59 refs.)

77-6784 In Vitro Malignant Transformation of Hamster Fetal Brain Cells by Methylnitrosourea. (Fre)

Markovits, P. (Fondation Curie-Institut du Radium, 26, rue d'Ulm, 75005 Paris, France); Levy, S.; Papadopoulos, D.; Nocentini, S.; Tripier, M. F.; Benda, P. *C R Acad Sci [D] (Paris)* 285(5): 623-626; 1977.

The effect of methylnitrosourea (MNU) on the in vitro malignant transformation and in vivo tumor-inducing capacity of a cell line with glial morphology was studied. The cell line was obtained from a primary culture of 14-day-old hamster fetal brain. Without MNU treatment, these cells remain non-transplantable for the first year of culture, but they undergo spontaneous malignant transformation in nude mice during the second year. Four-month-old cell cultures were treated with MNU (3 doses of 0.1, 0.5, 1, 5, or 10 $\mu\text{g/ml}$ at 20-day intervals or 2 doses of 25 or 50 $\mu\text{g/ml}$ at a 24-hr interval). Two to 6 mo after treatment, the glial cells were transplanted intraocularly or intracerebrally into hamsters ($0.5-1 \times 10^6$ cells/animal). Tumor induction rates, recorded for 150-180 days, were 0/7 for control cultures, 0/4 for cultures treated with 0.5-1 $\mu\text{g/ml}$ MNU, and 2/5 for those treated with 25-50 $\mu\text{g/ml}$. Transplantation 8-12 mo after treatment resulted in induction rates of 10/15 with controls and 0/6 with the 0.1- $\mu\text{g/ml}$, 1/5 with the 0.5-1- $\mu\text{g/ml}$, 4/7 with the 5-10- $\mu\text{g/ml}$, and 7/7 with the 25-50- $\mu\text{g/ml}$ -treated cells. In another series, cells were transplanted into nude mice 17 or 21 mo after treatment. Tumor induction rates were 5/6 with controls and 0/2 with 0.1- $\mu\text{g/ml}$, 1/3 with 0.5-10- $\mu\text{g/ml}$, and 7/7 with 25-50- $\mu\text{g/ml}$ -treated cells. The absence of malignant transformation after treatment with the lowest concentration (0.1 $\mu\text{g/ml}$) may indicate the elimination of cells susceptible to malignant transformation by the weak toxic action of MNU. The lowest dose also seemed to postpone spontaneous transformation. The MNU-treated cells retained their glial nature. (10 refs.)

77-6785 Chromosome Analyses of ENU-Induced Rat Neurogenic Tumors and Related Studies

(Meeting Abstract). (Eng.) Au, W. W. (Univ. Cincinnati, Cincinnati, OH). *Diss Abstr Int [B]* 38(4): 1657-1658; 1977. (no refs.)

- 77-6786 **Formation of Carcinogenic N-Nitroso Compounds from Carbendazim and Dodine Pesticides.** (Hun.) Surjan, A. (Országos Kozegészségügyi Intézet, Budapest, Hungary); Borzsonyi, M.; Nadasdi, L.; Pinter, A.; Csik, M. *Egeszsegtudomány* 21(1): 69-75; 1977.

The formation of carcinogenic N-nitroso compounds from carbendazim (methyl-2-benzimidazol carbamate, acute oral LD50 in mice: 11,000-15,000 mg/kg) and dodine (N-dodecylguanidine acetate, acute oral LD50 in mice: 1,200 mg/kg) was studied, and the carcinogenicity of these compounds was evaluated in male and female Swiss mice. The Griess reaction and infrared spectroscopy demonstrated the formation of N-nitroso compounds from carbendazim by nitrosation with methylene chloride and from dodine by nitrosation with 2 M sodium nitrite in 50% acetic acid. The N-nitroso compound formed from dodine was tentatively identified as dodecyl nitroso urea. Pregnant mice received daily 1/20 LD50 doses of carbendazim through a gastric tube and 0.05% sodium nitrite in their drinking water ad libitum during the second half of pregnancy. Malignant lymphomas were found in 33.3% of all mice and in 53.8% of their offspring. Another group of pregnant mice was treated in the same manner with 40 mg/kg of dodine per day. Eight of the 10 animals sacrificed during the first 170 days had a lymphoma, another had a pulmonary adenoma. In another group treated with 6 mg/kg, the incidence of lymphoma was 5/6. In the offspring of mothers treated with 40 mg/kg, 22/29 animals had a lymphoma, and 1 had a rectal adenocarcinoma. Among the offspring of the mothers treated with 6 mg/kg, 8/15 had a lymphosarcoma, 1 had a rectal adenocarcinoma. There were no tumors in untreated controls nor among the offspring of mothers treated with either test compound without sodium nitrite. The in vivo findings indicate the possibility of the formation of carcinogenic N-nitroso compounds from dodine and carbendazim in the presence of nitrite ions. (28 refs.)

- 77-6787 **Hydroxyurea: Induction of Breaks in Template Strands of Replicating DNA.** (Eng.) Walker, I. G. (Dept. Biochemistry, Univ. Western Ontario, London, Ontario, Canada N6A 5C1); Yatscoff, R. W.; Sridhar, R. *Biochem Biophys Res Commun* 77(1): 403-408; 1977.

The effects of hydroxyurea (HU) on replicating DNA were investigated in mouse L cells and secondary mouse embryo cells. Prolabeled L cells were treated with 5-fluoro-deoxyuridine followed by thymidine to release them synchronously into the S phase. HU was added after 30 min and, 30 min or 1, 3, or 4 hr later, the cells were removed for analysis. In another experiment, a mixture of four deoxynucleosides was added along with HU, and the cells were treated as before. Prolabeled secondary mouse cells were synchronized and treated with HU when in mid-S phase or prior to entering the S phase. The DNA's from HU-treated non-S phase cells, untreated non-S phase cells, and untreated S-phase cells all gave the same sedimentation profiles in a sucrose gradient.

The DNA from HU-treated S cells sedimented more slowly, indicating a lower mol wt and suggesting that the DNA had suffered single-strand breaks. An exposure time of > 30 min was required before single-strand breaks appeared in the template strand. The number of breaks reached a max by 1 hr and then declined until they were no longer apparent at 4 hr. Addition of the deoxynucleoside mixture along with HU to S-phase L cells considerably reduced the extent of single-strand breakage. The induction of breaks in the replicating DNA appears to be a consequence of the reduction of the deoxynucleoside triphosphate pool by HU but the molecular mechanism remains speculative. (19 refs.)

- 77-6788 **Changes in Nuclear RNA Transport Incident to Carcinogenesis.** (Eng) Schumm, D. E. (Dep. Physiological Chemistry, Ohio State Univ., Coll. Medicine, Columbus, OH 43210); Hanausek-Walaszek, M.; Yannarell, A.; Webb, T. E. *Eur J Cancer* 13(2): 139-147; 1977.

Sprague-Dawley rats were treated ip with 50 mg/kg of the hepatocarcinogens thioacetamide (9 injections) or dimethylnitrosamine (1 injection 24 hr after partial hepatectomy). The release (transport) of RNA from isolated liver nuclei to homologous or heterologous liver cytosol was evaluated in a cell-free system at various times after treatment. Within 2 hr cytosol from the carcinogen-treated animals enhanced the release of RNA from liver nuclei of untreated rats. This enhanced transport capacity of the cytosol persisted up to 4 mo after treatment; furthermore, the RNA transport from the liver nuclei of carcinogen-treated animals showed a partial loss of its ATP dependence. Although the capacity of cytosol from treated animals to support RNA transport dropped below control levels by 9 mo, the RNA transport from nuclei of the carcinogen-treated animals remained partially ATP independent. This ATP independence, which is also a characteristic of hepatoma nuclei, is not influenced by the age of the animal and it is not due to differences in the pool size of nuclear ATP or the requirement for polyadenylation of messenger RNA for transport. (32 refs.)

- 77-6789 **Time Dependence of Ethionine-induced Changes in Rat Liver Transfer RNA Methylation.** (Eng) Wainfan, E. (Lindsley F. Kimball Res. Inst., New York Blood Center, New York, NY 10021); Tschern, J. S.; Maschio, F. A.; Balis, M. E. *Cancer Res* 37(3): 865-869; 1977.

Ethionine-induced changes in liver transfer RNA (tRNA) methylation were investigated in female CFN Wistar rats who received daily ip injections of 250 mg/kg DL-ethionine (E) and 120 mg/kg adenine (A) for up to 14 days. Sodium pentobarbital (50 mg/kg) was given 2 days before sacrifice to minimize RNase activity in the liver. After 2 days of E + A, methyl-deficient tRNA and subnormal levels of tRNA-methylating enzymes were found in the rat livers. A alone had no effect on methylation. When the two compounds were

administered for longer periods, liver tRNA-methylating enzyme activity measured in vitro gradually increased and exceeded that of controls. Concurrently, the relative methyl deficiency of liver tRNA decreased. Liver tRNA from animals treated with E for 7 days could accept only about 40% as many methyl groups as tRNA from animals that had received E for only 2 days (when changes were first noted). No further significant change in the methyl deficiency of the tRNA was seen when E administration was extended to 14 days. Enzyme preparations from E-treated rat livers contained dialyzable substances that inhibited tRNA methylases and altered the base specificity of these enzymes. Although S-adenosylhomocysteine and S-adenosylethionine were present in the preparations, neither could account for the changes in specificity. It is not certain whether the increases in tRNA-methylating enzyme activity are due to increased enzyme synthesis, altered enzymes, or changes in the levels of the substances that modulate this activity. (23 refs.)

77-6790 Inhibition of DNA Methylation by S-Adenosylethionine with the Production of Methyl-deficient DNA in Regenerating Rat Liver. (Eng) Cox, R. (Dept. Biochemistry, Univ. Tennessee Center Health Sciences, Memphis, TN 38104); Irving, C. C. *Cancer Res* 37(1): 222-225; 1977.

Male Sprague-Dawley rats were administered the hepatocarcinogen ethionine (E: 300 mg/kg po) 17 hr after partial hepatectomy. Six hours later, hepatic S-adenosylethionine levels were 30- to 40-fold greater than the S-adenosylmethionine level. A tenfold ratio of S-adenosylethionine to S-adenosylmethionine still persisted at 24 hr after E administration. E also produced a 30% inhibition of DNA synthesis as measured by the incorporation of methyl-³H-thymidine at 23-24 hr after partial hepatectomy (6-7 hr after E administration). DNA synthesized during this interval was methyl-deficient as judged by the reduced incorporation of radioactivity from L-methyl-³H-methionine into 5-methylcytosine residues of DNA. In an assay for DNA methylation in vitro using whole nuclei, the methyl-deficient DNA was methylated by S-adenosylmethionine eight times more than was control DNA; the DNA methylation was competitively inhibited by S-adenosylethionine. These data suggest that S-adenosylethionine, formed in vivo from E, competitively inhibits the methylation of DNA in vivo by S-adenosylmethionine, resulting in the production of methyl-deficient DNA. (26 refs.)

77-6791 Long-Term Toxicity of the Surfactant α -Olefin Sulphonate (AOS) in the Rat. (Eng) Hunter, B. (Huntingdon Res. Centre, Huntingdon, England); Benson, H. G. *Toxicology* 5(3): 359-370; 1977.

Groups of 100 CFY rats (50 males and 50 females) of Sprague-Dawley origin were fed diets containing the surfactant α -olefin sulfonate (AOS) at levels of 1,000, 2,500, and 5,000

ppm over a 104-wk period. Ophthalmoscopic examinations and laboratory investigations during treatment revealed no abnormalities that could be attributed to AOS. No changes in pathology or organ wts were observed in the treated rats following sacrifice at 104 wk. Pancreatic islet cell tumors occurred at a high incidence in males (4/50) receiving 1,000 ppm AOS; thyroid tumors were higher among females (5/50) receiving 2,500 ppm; and adrenal tumors were higher in male rats (8/50) receiving 2,500 ppm. However, these incidences do not appear to be connected with AOS treatment because of the absence of any dose-related trend and because of previous data showing similar incidences in control CFY rats. In view of these results, AOS appears to present no public or environmental hazard. (22 refs.)

77-6792 Repair Replication and Sister Chromatid Exchanges as Indicators of Excisable and Nonexcisable Damage in Human (Xeroderma Pigmentosum) Cells. (Eng.) Cleaver, J. E. (Lab. Radiobiology, Univ. California, San Francisco, CA 94143). *J Toxicol Environ Health* 2(6): 1387-1394; 1977.

Human fibroblasts from normal donors and from excision repair-deficient xeroderma pigmentosum (XP) patients were exposed to small volumes of various alkylating carcinogens, including 4-nitroquinoline 1-oxide, dimethyl sulfate, methylnitrosourea, and ethylnitrosourea (ENU). Relative amounts of repair replication were measured with ³H-bromodeoxyuridine (³H-BUDR, 20 μ Ci/ml, 10 μ M). Induced sister chromatid exchanges (SCE's) were measured by the Hoechst 33258-Giemsa method using 20 μ M BUDR. Immediately after exposure, both cell types underwent normal amounts of repair replication of excisable damage. However, some damage from ENU exposure was still being repaired in XP cells 20-25 hr after exposure. The frequency of the SCE's was higher in XP cells than in normal cells, and it showed a high degree of correlation with the amount of unexcised damage in DNA. Thus, SCE measurement may be a more sensitive indicator of the potential carcinogenicity of a chemical. (21 refs.)

77-6793 Development of a Focus Assay Model for Transformation of Hamster Cells In Vitro by Chemical Carcinogens. (Eng) Casto, B. C. (BioLabs, Inc., Northbrook, IL 60062); Janosko, N.; DiPaolo, J. A. *Cancer Res* 37(10): 3508-3515; 1977.

A reproducible, quantitative focus assay for transformation of freshly isolated diploid Syrian hamster embryo cells by chemical carcinogens was developed by modifying the technique used for the colony assay. The transformed foci are observed against a normal cell background, and the transformed morphology is verified by stereomicroscopy; consequently, the number of areas that need to be examined is greatly reduced relative to the colony assay. Transformed cell foci were induced in hamster secondary cells after treatment

for 6 days with acetoxyacetylaminofluorene, alfatoxin B₁, benzo(a)pyrene, β -propiolactone, dibenz(a,h)anthracene, ethyl methanesulfonate, 3-methylcholanthrene, methyl methanesulfonate, or N-methyl-N'-nitro-N-nitrosoguanidine. Three types of foci were observed: fibroblastlike, epithelial-like, and round cell foci. Cells from isolated, transformed foci grew to higher cell densities than controls, lacked oriented growth, and formed tumors when injected into weanling hamsters. The frequency of focus formation ranged from four to seven foci/10⁵ surviving cells at chemical concentrations that killed < 90% of the cells. The transformation frequency was independent of cell number from 5×10^1 to 5×10^4 cells/dish, but it depended on chemical concentration, length of treatment, and time of chemical addition after cell transfer. The expression of transformed foci was inhibited by reduction of fetal bovine serum from 10% to 1%, substitution of calf serum for fetal bovine serum, or addition of dextran sulfate, diethylaminoethyl dextran, or 0.5% agar to the medium within 3 days of chemical treatment. (20 refs.)

- 77-6794 Comparative Study of the Carcinogenic Activities of Nas and Some Chemical Carcinogens when Introduced into the Buccal Pouch of the Syrian Hamster.** (Eng) Milievskaja, I. L. (Dept. Epidemiology Malignant Tumours, Inst. Experimental and Clinical Oncology, Acad. Medical Sciences USSR, Karsirskoe sosse 6, Moscow, USSR); Kiseleva, N. S. *Bull WHO* 54(6): 607-614; 1977.

The carcinogenic effects of nas, 7,12-dimethylbenz[a]anthracene (DMBA), dimethylnitrosamine (DMNA), diethylnitrosamine (DENA) and N-methyl-N-nitrosourea (MNU) were investigated after administration to the buccal pouch of Syrian hamsters. There were six groups of hamsters. Group I received nas either as a dry powder or as a 50% suspension in sunflower oil throughout life. The total dose ranged from 6.2 to 147.5 g. In the second group, there were two subdivisions: a single dose of 100 μ g benzene in a 0.1 soln was applied in the first; in the second, a similar dose was applied plus a daily form of the dry powdered dose of nas as in group I starting 7 wk after the DMBA administration. Groups III, IV and V received DMNA, DENA and MNU, respectively, in saline, at a dose of 0.1 mg/animal twice a wk to a max dose of 7.5 mg in < 9 mo. Group 6 served as a control. No tumors were found in the buccal pouch of animals receiving nas, but remote tumors were found in 18.8% of these animals; these were most frequently noted in the liver (13/33) followed by the adrenals (6), forestomach (5), and uterus (4). Tumors developed in 3/11 of those animals receiving DMBA only that survived until tumor appearance. One of these was in the buccal pouch and the others were in the forestomach. Tumors developed in 6/11 hamsters receiving DMBA + nas that survived until tumor appearance; five of these tumors were papillomas of the forestomach and one was a cystic epithelioma of the lower jaw. Five tumors, all in the liver, were noted in six animals receiving DMNA that survived until tumor appearance. No tumors were observed in animals receiving DENA. Tumors developed in 20/25 ani-

mals receiving MNU that survived until tumor appearance. Of these, 13 were in the buccal pouch, 11 in the forestomach, 1 in the liver and 1 in the adrenals. In seven cases, buccal tumor was combined with another neoplasm. The significance of these findings is discussed in terms of the carcinogenicity of nas. (38 refs.)

- 77-6795 In Vitro Studies of Chemical Mutagens and Carcinogens. I. Stability Studies in Cell Culture Medium.** (Eng.) Jensen, E. M. (EG&G/Mason Res. Ins. 1530 E. Jefferson St., Rockville, MD 20852); LaPolla, R. J.; Kirby, P. E.; Haworth, S. R. *J Natl Cancer Inst* 59(3): 94-944; 1977.

A quantitative microbial mutagenesis assay was used to study the stability of known mutagenic and carcinogenic compounds in Dulbecco's modification of Eagle's minimum essential medium (pH 7.2-7.4, 37 C) supplemented with glutamine (2 millim) and fetal bovine serum (15%). The biological half-lives of 10 direct-acting carcinogenic compounds were: 8 min (N-methyl-N-nitrosourea, 1 mg/ml); 14 min (N-methyl-N'-nitro-N-nitrosoguanidine, 1 μ g/ml); 19 min (streptozotocin, 5 μ g/ml); 50 min (N-methyl-N-nitrosourea, 0.02 μ l/ml); 1.8 hr (propane sultone, 80 μ l/ml); 2.2 hr (ethylmethane sulfonate, 50 μ l/ml); 5 hr (nitrogen mustard, 2.5 mg/ml); 8.5 hr (methyl methane sulfonate, 10 μ l/ml); 12 hr (nitrogen mustard hydrochloride, 4 mg/ml); and 67 hr (4-nitroquinoline 1-oxide, 3 μ g/ml). The six procarcinogens tested [2-aminoanthracene, 4-aminobiphenyl, benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene, 2-aminofluorene, and 4-(o-tolylazo)-o-toluidine] showed no inactivation after 3 wk incubation at concentrations of 3 μ g/ml, 1 mg/ml, 30 μ g/ml, 200 μ g/ml, and 200 μ g/ml, respectively. (1 refs.)

- 77-6796 The Environmental Fate of Three Carcinogens: Benzo(a)pyrene, Benzidine, and Vinyl Chloride Evaluated in Laboratory Model Ecosystems.** (Eng) Lu, P. Y. (Dept. Entomology and Inst. Environmental Studies, Urbana, IL 61801); Metcalf, R. L.; Plummer, N.; Mandel, D. *Arch Environ Contam Toxicol* 6(2-3): 129-142; 1977.

The degradation, environmental fate, bioaccumulation, and food chain transfer of radiolabeled benzo(a)pyrene (BP), benzidine (BD), and vinyl chloride (VC) were evaluated in two laboratory model ecosystems. In a close aquatic system, 0.002 ppm BP and 0.008 ppm BD were applied directly to the water and allowed to pass through an aquatic food chain. Their transfer and degradation were observed over a 3-day period. In a terrestrial-aquatic ecosystem, 0.2 mg of BP and BD, either alone or with 1.0 mg piperonyl butoxide, were topically applied in acetone solution to *Sorghum vulgare* seedlings, representing chemical fallout. They were then allowed to pass through a food chain. The resulting food chain byproducts

were then allowed to interact in the ecosystem over a 33-day period. It was shown that BP is highly lipophilic and it can bioaccumulate to potentially hazardous levels. This problem was intensified in snails and other organisms deficient in microsomal oxidase, or when there was a presence of mixed function oxidase inhibitors. BD was not bioaccumulated or transferred through food chains to high levels. BD levels were not affected appreciably by the presence of mixed function oxidase inhibitors. Vinyl chloride did not bioaccumulate or transfer appreciably through the food chains, at least at the ordinary temperatures studied due to its high volatility. There was an excellent correlation between bioaccumulation and octanol/water partition, illustrating that this property and water solubility can be a predictive value in environmental toxicological studies. (19 refs.)

77-6797 Effect of High-Fat Diet on Colon Carcinogenesis in F344 Rats Treated with 1,2-Dimethylhydrazine, Methylazoxymethanol Acetate, or Methylnitrosourea. (Eng) Reddy, B. S. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595); Watanabe, K.; Weisburger, J. H. *Cancer Res* 37(11): 3564-3569; 1977.

Male bred male F344 weanling rats were fed semipurified diets containing 20% or 5% beef fat. At 7 wk of age, animals except controls were given 1,2-dimethylhydrazine (DMH, 150 mg/kg sc 1 dose), methylazoxymethanol acetate (MAM acetate, 35 mg/kg ip, 1 dose), or methylnitrosourea (MNU, 2.5 mg/rat/wk intraperitoneally, 2 doses). The animals were autopsied 35 wk later. No major differences were observed in the frequency (number of rats with tumor) of DMH- or MAM acetate-induced duodenal, ear duct, and kidney tumors between rats fed diets containing 20% or 5% fat. However, the animals fed the 20% fat diet and treated with DMH, MAM acetate, or MNU had a higher frequency of colon tumors than rats fed the 5% fat diet and treated similarly. Dietary fat at the 20% level was associated with an increased incidence of MAM acetate- or MNU-induced colon tumors (number of tumors/tumor-bearing rat). However, in rats treated with DMH, the incidence of colon adenomas and adenocarcinomas did not differ significantly. (29 refs.)

77-6798 Investigation of Mutagenic Effects of Products of Ozonation Reactions in Water. (Eng) Conroy, J. A. (Office Water Supply, U.S. Environmental Protection Agency, Washington, DC 20460); Simmon, V. F.; McGee, R. J. *Ann NY Acad Sci* 298: 124-140; 1977.

Twenty-eight compounds were subjected to extensive ozonation in water (ie, conditions more severe than those used in water treatment), and the toxicity and mutagenicity of the reaction products were tested in *Salmonella typhimurium* and *Saccharomyces cerevisiae*. Only ethanol, benzidine, phe-

nol, 1,1-diphenylhydrazine, hydroquinone, 2,4-dinitrotoluene, and nitrilotriacetic acid showed some level of mutagenicity after ozonation. The activity usually resulted only after prolonged ozone exposure, was not dose-related, and was not always repeatable. (5 refs.)

77-6799 Rat Liver Post-microsomal D-T Diaphorase: Activation of the Enzymes by Two Carcinogens. (Eng) Schor, N. A. (Dept. Pathology, Tulane Univ. Sch. of Medicine, New Orleans, LA 70112); Boh, E. *Res Commun Chem Pathol Pharmacol* 16(1): 179-182; 1977.

Male Sprague-Dawley rats (300 g) were sacrificed 24 hr after being administered acetylaminofluorene or 7,12-dimethylbenz(a)anthracene (10 mg/100 g) by an intragastric tube. The two carcinogens increased the activity of the rat liver enzyme D-T diaphorase at least two-fold. Microsomal NADPH cytochrome C reductase activity was not altered. D-T diaphorase may participate in the detoxification and/or activation of the carcinogens, but its exact relationship to these compounds remains obscure. (9 refs.)

77-6800 Respiration and Oxidative Phosphorylation in Rat Kidney Mitochondria under the Influence of a Carcinogen. (Rus.) Kozhevnikova, E. P. (Dept. Pathophysiology, Orenburg Medical Inst., Orenburg, USSR); Beliaeva, N. M.; Matchin, G. A. *Vopr Onkol* 23(8): 100-101; 1977.

Respiration and oxidative phosphorylation by kidney mitochondria were studied in random-bred rats treated with 3-methylcholanthrene (MC) or dimethylnitrosamine (DMNA). Oxygen consumption in the mitochondria of kidneys without morphological signs of tumor was assessed 6 and 10 mo after MC administration and 4 and 8 mo after DMNA administration. The respiratory control index in the MC-treated rats was decreased in the presence of succinic acid and glutamic acid, but in DMNA-treated rats it was decreased only in the presence of glutamic acid. (7 refs.)

77-6801 Hepatic Cell Loss and Proliferation Induced by N-2-Fluorenylacetylamide, Diethylnitrosamine, and Aflatoxin B₁ in Relation to Hepatoma Induction. (Eng.) Nishizumi, M. (Dept. Public Health, Faculty Medicine, Kyushu Univ., Fukuoka 812, Japan); Albert, R. E.; Burns, F. J.; Bilger, L. *Br J Cancer* 36(2): 192-197; 1977.

Carcinogenicity, early cell toxicity, and parenchymal cell proliferation were studied in the livers of rats receiving aflatoxin B₁ (1 ppm in pelleted food), diethylnitrosamine (DEN; 20 ppm in drinking water), and N-2-fluorenylacetylamide (FAA; 300 ppm in pelleted food) for 15 wk. On a molecular basis, aflatoxin B₁ was 90 times as carcinogenic as FAA and 24 times as carcinogenic as DEN,

although for equal magnitudes of cell proliferation and loss aflatoxin B₁ was the least potent carcinogen. For a given level of carcinogenicity, FAA was more potent than DEN in causing loss of hepatic DNA and increasing the parenchymal cell labeling index. DEN and aflatoxin B₁ produced about the same degree of DNA loss and parenchymal cell labeling, but DEN was the more potent carcinogen. When carcinogenicity was compared for approx equal levels of early hepatic cell destruction and proliferation, the potency of the three agents could be ranked in the order DEN > FAA > aflatoxin B₁. (11 refs.)

- 77-6802 **Comutagenic Action of Norharman and Harman.** (Eng) Nagao, M. (Natl. Cancer Center Res. Inst., 5-1-1, Tsukiji, Chuo-ku, Tokyo 104, Japan); Yahagi, T.; Kawachi, T.; Sugimura, T.; Kosuge, T.; Tsuji, K.; Wakabayashi, K.; Mizusaki, S.; Matsumoto, T. *Proc Jpn Acad* 53(2): 95-98; 1977.

A modified Ames test showed that norharman and harman enhanced the mutagenic activity of two γ -carboline derivatives (3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole and 3-amino-1-methyl-5H-pyrido[4,3-b]indole), 4-dimethylaminoazobenzene, benzo(a)pyrene, 4-dimethylaminostilbene, and N-2-fluorenylacetylamide in *Salmonella typhimurium*. The comutagenic action of norharman and harman was observed only with mutagens that required metabolic activation by an S-9 mix containing NADPH, NADH, and ATP. The possibility that the two substances are cocarcinogenic with natural carcinogens is discussed. (7 refs.)

- 77-6803 **Evaluation of the Mutagenic Activity of Chromium Compounds.** (Rus) Bigaliev, A. V. (Medical Inst., Aktiubinsk, USSR); Elemesova, M. Sh.; Turebaev, M. N. *Gig Tr Prof Zabol* (6): 37-40; 1977.

The mutagenic effects of potassium bichromate and other chromium compounds that occur in factories in the form of aerosols were studied by cytogenetic tests using human embryonal fibroblast and peripheral lymphocyte cultures. When added to fibroblast cultures at a concentration of 0.3 μ g/ml, potassium bichromate totally suppressed mitosis. Concentrations of 0.03 and 0.15 μ g/ml decreased the mitotic index to 4.2-4.6 vs 6.5 in control cultures, and they increased the number of cells with aberrant chromosomes from 0.85%-2.52% (controls) to 2.21%-5.73%. Peripheral lymphocyte cultures from men and women who had been exposed to chromium aerosols for 1 to 8+ yr showed that all compounds (monochromate, sodium bichromate, chromium oxide, and chromium trioxide) caused a significant ($p < 0.01-0.05$) increase in the percentage of cells with aberrant chromosomes compared with cultures of cells from unexposed subjects. The percentage increased with the length of occupational exposure, and

it was highest in workers exposed to hexavalent chromium compounds (5.44%-9.40%). The findings indicate the mutagenic risk of industrial chromium-containing aerosols. (5 refs.)

- 77-6804 **Retention and Tissue Distribution of $^{210}\text{Pb}(\text{NO}_3)_2$ Administered Orally to Infant and Adult Monkeys.** (Eng) Willes, R. F. (Toxicology Res. Div., Food Directorate, Tunney's Pasture, Ottawa, Canada); Lok, E.; Truelove, J. F.; Sundaram, A. J. *Toxicol Environ Health* 3(3): 395-406; 1977.

The retention and tissue distribution of ^{210}Pb were studied in 10-day-old, 150-day-old, and adult monkeys. $^{210}\text{Pb}(\text{NO}_3)_2$ was administered to the monkeys by gavage after a 12-hr fast, and ^{210}Pb excreted in urine and feces was monitored for 96 hr. All monkeys were necropsied 96 hr after dosing, and the ^{210}Pb concentration of various tissues was determined. Infant monkeys retained 64.5% and 69.8% of the po administered ^{210}Pb at 10 and 150 days of age, respectively, but adult monkeys retained only 3.2%. Blood ^{210}Pb levels 96 hr after dosing did not vary significantly with age. Of the ^{210}Pb contained in blood, 98%-99% was found in blood cells and 1%-2% in blood plasma; 5%-8% of the Pb in blood cells was bound to blood cell membranes. None of these parameters nor the percentage of the lead dose excreted in urine varied significantly with age. Both the tissue Pb concentrations and tissue Pb:blood Pb ratios were significantly higher in the bones of the infants than those of the adults. Brain Pb:blood Pb ratios were significantly greater in 10-day-old infants than 150-day-old infants or adults. (30 refs.)

- 77-6805 **Nonneoplastic and Neoplastic Changes in the Kidneys and Other Organs of Rodents Chronically Fed Lead Acetate and Sulfathiazole.** (Pol) Waszynski, E. (Zaklad Anatomii Patologicznej Instytutu Biostruktury AM, ul. Leszczynskich 20, 64-100 Leszno, Poland). *Patol Pol* 28(1): 101-111; 1977.

The effects of lead acetate (LA) and/or sulfathiazole (ST) on the kidneys of Wistar rats and F₁(RHH x C57BL) mice were studied. The rats received daily doses of 3 mg LA and 54 mg ST po, and the mice received daily doses of 0.3 mg LA and 6 mg ST po for 180 days. LA alone resulted in injuries to the renal cortex and benign and malignant proliferative processes, but ST caused changes mainly in the renal pelvis and medulla, with degeneration of the tubular epithelium. Additive effects were noted in animals fed LA + ST. ST alone produced no precancerous changes in the rat kidney, but they were observed in 7/42 animals fed LA, 13/43 animals fed both compounds, and 0/34 control animals. Tumor incidence was 0/43 in the ST group, 11/42 in the LA group, 8/43 in the ST + LA group, and 0/34 in the controls. The tumors included 12 adenomas, 1 solid adenocarcinoma, and 6 clear cell adenocarcinomas with papillomatous elements. LA and

ST produced less marked changes in mice than in rats. The findings indicate a tumor-inhibiting effect of ST. (18 refs.)

- 77-6806 **Gonadotropic Function of the Pituitary Gland in the Induction and Prevention of Testicular Tumors in Rats.** (Rus) Dmitriev, V. N. (State Medical Inst., Izhevsk, USSR). *Vopr Onkol* 23(9): 52-55; 1977.

The gonadotropic function of the pituitary gland was studied in sexually mature rats during the induction of germinal tumors (teratomas and seminomas) by intratesticular injection of copper sulfate solution and interstitial cell tumors by subtotal castration. During germinal tumor induction, pituitary gland production of follicle-stimulating hormone (FSH) was increased markedly, that of luteinizing hormone (LH) was reduced. In contrast, a sharp and persistent increase in the LH level was seen during the induction of interstitial cell tumors. Suppression of FSH and LH production prevented the induction of germinal and interstitial cell tumors, respectively. (10 refs.)

- 77-6807 **Mechanisms of Dissolution of Nickel Subsulfide in Rat Serum.** (Eng) Kasprzak, K. S. (Radiochemical Lab., Dept. General Chemistry, Poznan Polytechnical Univ., Poznan, 60-965, Poland); Sunderman, F. W. *Res Commun Chem Pathol Pharmacol* 16(1): 95-108; 1977.

The chemical mechanisms whereby nickel subsulfide (α - Ni_3S_2) becomes dissolved in body fluids were investigated by incubating α - Ni_3S_2 dust in water, rat serum, and a rat serum ultra-filtrate at 37 C for 2 wk. The sediments that remained were examined by x-ray diffractometry and compared with the x-ray diffraction pattern of the original α - Ni_3S_2 dust. The were measured by liquid scintillation counting. The solubilization of Ni(II) from α - Ni_3S_2 in rat serum required the presence of O_2 and involved three reactions. α - Ni_3S_2 was partially oxidized to β -NiS and $\text{Ni}(\text{OH})_2$, β -NiS was further oxidized to nickel (Ni^{+2}) and sulfate ions, and $\text{Ni}^{+2} + \text{Ni}(\text{OH})_2$ reacted with serum ligands (albumin and amino acids) to form soluble Ni(II) complexes. The solubilization of ^{63}Ni from α - Ni_3S_2 was initially more rapid in rat serum than in the serum ultrafiltrate or in water. After 2 days of incubation, the dissolution of α - $^{63}\text{Ni}_3\text{S}_2$ in the three media became progressively retarded, probably due to the deposition of insoluble surface coatings of β - ^{63}NiS and $^{63}\text{Ni}(\text{OH})_2$ on the $^{63}\text{Ni}_3\text{S}_2$ particles. (23 refs.)

- 77-6808 **Effects of Arsenite on DNA Repair in *Escherichia coli*.** (Eng) Rossman, T. G. (Dept. Environmental Medicine, New York Univ. Medical Center, New York, NY 10016); Meyn, M. S.; Troll, W. *Environ Health Perspect* 19: 229-233; 1977.

Several strains of *Escherichia coli*, which differed only in repair capacity, were grown in medium containing sodium arsenite to determine the effects of this compound on DNA repair following UV irradiation. Concentrations of arsenite up to 5 milliM had no effect on the viability of unirradiated *E. coli*; at ≥ 1 milliM, however, the colony size was smaller, indicating an inhibition of growth rate. Concentrations of ≥ 0.1 milliM decreased the survival of irradiated wild-type WP_2 cells and increased the survival of irradiated strain WP_5 cells. Furthermore, arsenite decreased the absolute mutation frequency and number of mutations per survivor at all UV exposures in the WWP_2 strain, which lacks excision repair. This suggests that arsenite inhibits one or more steps in the post-replication repair pathways. The effect of arsenite on the survival of UV-irradiated *E. coli* increased with increasing irradiation. Arsenite must also be present under conditions of cell growth in order to decrease postirradiation survival. The cellular functions most sensitive to arsenite inhibition were β -galactosidase induction and RNA synthesis. It was concluded that inhibition of mutagenesis following UV irradiation is the result of inhibition of messenger RNA (mRNA) synthesis, since enzyme induction requires the synthesis of new mRNA. (20 refs.)

- 77-6809 **Experimental Studies on Arsenic Absorption Routes in Rats.** (Eng) Dutkiewicz, T. (Environmental Pollution Abatement Center, J. Krasickiego 2, 40832 Katowice, Poland). *Environ Health Perspect* 19: 173-177; 1977.

Female Wistar rats were given pentavalent inorganic arsenic (0.1-4.0 mg/kg) in the form of sodium arsenate either iv, intratracheally (i.t.), gastrointestinally (gi), or topically, to the skin. The content of As in the tissues was similar for the iv and i.t. routes and for the gi and skin resorption routes. After 24 hr, the tissue content of As was $< 20\%$ of the applied dose, except for skin application, where $> 50\%$ of the dose was outside the blood due to its deposit at the application site. Increases in liver and spleen As concentrations were slower after topical and gi administration than after iv or i.t. administration. Skin resorption was 1.14-33.1 $\mu\text{g}/\text{cm}^2/\text{hr}$ for 0.01-0.2 M aqueous solutions of As salts. There were considerable amounts of As bound to RBC, independent of the route of administration. The concentration of As in the blood was proportional to the absorbed dose over the range given and did not change over time, indicating that As accumulates in the RBC. As was eliminated mainly via the urine and feces, although the urine: feces ratio varied considerably for the different routes. The elimination occurred in three phases after the iv and i.t. routes and in two phases after the gi and topical routes. Upon continuous administration, elimination via the urine reached a constant percentage of the daily intake. Administration of selenium salts as an accelerating agent increased the urinary elimination of As in the slow phase by 20%-30%. These relations could serve as

potential baselines for the development of As exposure indicators in man. (8 refs.)

- 77-6810 Effect of the Combined Action of Selenium and Arsenic on Suspension Culture of Mice Fibroblasts.** (Eng) Rossner, P. (Inst. Hygiene and Epidemiology, Medical Faculty Hygiene, Charles Univ., 100 42 Prague, Czechoslovakia); Bencko, V. Havrankova, H. *Environ Health Perspect* 19: 235-237; 1977.

The growth of L₁15 mouse fibroblasts in suspended culture in their logarithmic phase was observed following the isolated and combined action of sodium arsenite (10^{-5} to 10^{-11} M) and sodium selenite (10^{-5} to 10^{-11} M) for 5 days. The growth curve showed that Se and As alone at concentrations of 10^{-7} M were nontoxic, with values similar to those of control cultures. When the two were combined, decreasing levels of As enhanced its protective effect against Se in the range of concentrations used, whereas a low protective effect of Se against As was observed at these levels. It was concluded that cell cultures are most suitable for a toxicological model study of the combined effects of arsenic and selenium. (5 refs.)

- 77-6811 Effects of Concurrent Administration of Lead, Cadmium, and Arsenic in the Rat.** (Eng) Mahafey, K. R. (Div. Nutrition-HFF-260, Food and Drug Admin., 200 C. St., S.W., Washington, DC 20204); Fowler, B. A. *Environ Health Perspect* 19: 165-171; 1977.

A total of 168 male albino Sprague-Dawley rats were fed nutritionally adequate diets containing 0 or 200 ppm lead as lead acetate, 50 ppm cadmium as cadmium chloride, and/or 50 ppm arsenic as sodium arsenate or arsanilic acid for 10 wk. Food intake and wt gain were reduced when Cd or As were fed, but these effects were more pronounced when Cd and As were combined. Pd did not adversely affect wt gain or food intake. All three metals increased the number of circulating RBC, with combinations of the metals usually producing an increase over and above that produced by either metal alone. Only As alone was capable of reducing both Hb and hematocrit, although the greatest decreases were seen with Pb + Cd and Cd + organic As. The number of peripheral WBC was decreased significantly only by Cd. Urinary δ -amino-levulinic acid excretion was greatly increased by Pb, but this increase was reduced by Cd. Blood analysis showed values within the normal range for blood urea nitrogen, creatinine, cholesterol, calcium, albumin, total protein, and bilirubin. Pb increased serum uric acid concentration. Only Cd and As decreased serum alkaline phosphatase activity, and Cd + As enhanced this reduction. Elevated levels of Pb increased both kidney wt and the kidney wt: body wt ratio. The liver wt:body wt ratio was decreased only by Cd. Electron microscopy demonstrated that morphological changes in kidneys of animals exposed to combinations of Cd and either arsenical were relatively slight. Significant interactions

between all three metals were found to be relatively infrequent; the most consistent ones were between Pb and Cd and between Cd and As. Generally, the presence of the other metals reduced the magnitude of the Pb effect. (26 refs.)

- 77-6812 Effect of Chronic Action of Cadmium Sulfate on Blood Serum Parameters and Liver and Kidney Morphology in Rats.** (Pol) Dominiczak, K. (Zaklad Higieny PAM, ul. Noakowskiego 15/2, 70-38 Szczecin, Poland); Mikulski, T. *Med Pracy* 28(3): 179-187; 1977.

Sixty male Wistar rats weighing 180-220 g were given weekly doses of 0.4 mg/kg of cadmium sulfate sc for 6-12 mo. The animals were sacrificed after 6, 9, and 12 mo to study certain biochemical parameters of the blood serum and morphological changes in the liver and kidneys. From 9 mo on, there were significant changes in the blood serum: a reduced albumin level and increased globulin, urea, alkaline phosphatase, SGPT, and SGOT levels. The morphological changes, which were parallel to the biochemical changes, included hepatocyte degeneration, lesions of the renal parenchyma, and connective tissue proliferation. The degenerative changes were more pronounced in the liver than in the kidneys. (29 refs.)

- 77-6813 Resolution of Two Forms of Cytochrome P-450 from Liver Microsomes of Rabbits Treated with 2,3,7,8-Tetrachlorodibenzo-p-dioxin.** (Eng) Johnson, E. F. (Dept. Biochemistry, Scripps Clinic and Res. Foundation, La Jolla, CA 92037); Muller-Eberhard, U. *J Biol Chem* 252(9): 2839-2845; 1977.

Chromatography of male New Zealand rabbit liver microsomal preparations from animals treated 5 days previously with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD: 94 nanomoles ip) resulted in the isolation of two forms of cytochrome P-450. The yield of the major form (P-450c) was approx three times that of the minor one (P-450ab). The reduced CO difference spectra and the n-octylamine difference spectra for these two forms were different; the spectra for P-450c corresponded to those from TCDD-treated animals, but the spectra for P-450ab corresponded to those of untreated animals. Electrophoresis of P-450c showed a single band with an Mr of 54,000; the minor form contained several peptides with an Mr of 60,000 and 47,000. Antibody produced against P-450c inhibited microsomal acetanilide hydroxylation by 80%, but it did not cross-react with P-450ab. Furthermore, it did not inhibit the hydroxylation of 3,4-benzpyrene or coumarin, the N-demethylation of aminopyrine, or the O-deethylation of 7-ethoxycoumarin catalyzed by rabbit liver microsomes. It is concluded that at least two forms of cytochrome P-450 exist in rabbit liver microsomes following TCDD treatment and that they differ in immunological properties and catalyze different monooxygenase activities. (30 refs.)

77-6814 **Increased Incidence of Neoplasms in Rats Exposed to Low Levels of 2,3,7,8-Tetrachlorodibenzo-p-dioxin.** (Eng) Van Miller, J. P. (Dept. Pathology, Univ. Wisconsin, Madison, WI 53706); Lalich, J.; Allen, J. R. *Chemosphere* 6(9): 537-544; 1977.

The toxicity and carcinogenicity of low dietary levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) were investigated in male Sprague-Dawley rats divided into groups of 10 animals each and fed diets containing TCDD at 1, 5, 50, or 500 parts/trillion (ppt; 10^{-12} g CDD/g food) or 1, 5, 50, 500, or 1,000 ppb (10^{-9} g CDD/g food). All animals given the three highest doses died within 2-4 wk. Necropsy revealed severe liver necrosis, cellular proliferation in the bile ducts, atrophy of the thymus and spleen, and hemorrhage in the gastrointestinal tract. Of the animals fed subacute doses (5-500 ppt and 5 or 5 ppb), 23 developed neoplasms by 78 wk. The types of tumors included squamous cell lung tumors, ear duct carcinoma, lymphocytic leukemia, retroperitoneal histiocytoma, cholangiocarcinoma, angiosarcoma, fibrosarcoma and fibroma, astrocytoma, and glioblastoma. This variety of neoplasms is not consistent with the action of many known chemical carcinogens, which suggests that TCDD may be a promotor rather than an inducer of neoplastic change. (15 refs.)

77-6815 **In Vitro Covalent Binding to DNA of the Ultimate Carcinogen N-Acetoxy-N-4-acetylaminobiphenyl.** (Eng) Lang, M. C. (Laboratoire de Biophysique, Institut de Biologie Moléculaire et Cellulaire du CNRS, 15 rue Descartes, 67084 Strasbourg Cedex, France); Fuchs, R. P.; Daune, M. P. *FEBS Lett* 81(1): 101-104; 1977.

The amount of biphenylation and acetylation that occurs during the binding of N-acetoxy-N-4-acetylaminobiphenyl (N-AcO-AABP) to DNA was investigated as a function of the DNA secondary structure using native and heat-denatured DNA. N-AcO-AABP was double-labeled: the N-acetoxy group was labeled with ^3H and the N-acetyl group was labeled with ^{14}C . The concentration of N-AcO-AABP used was 2, 4, or 8 times that of the nucleotides in DNA during incubation. The biphenylation was dependent upon the secondary structure, since heat-denatured DNA reacted four to five times more than native DNA. With native DNA, however, the biphenyl derivative was less reactive than the phenanthryl analog, in contrast with all the other N-acetoxy-N-arylacetamides tested to date. Acetylation was followed by the incorporation of ^3H into the DNA; this reaction also occurred with native and heat-denatured DNA. It is not known whether the observed thermal destabilization of the DNA following reaction with N-AcO-AABP is due to biphenylation and/or acetylation. (12 refs.)

77-6816 **A Preliminary Pharmacokinetic Model for Several Chlorinated Biphenyls in the Rat.** (Eng.) Lutz, R. J. (Chemical Engineering Section, Biomedical Engineering and Instrumentation Branch, Building 13, Room 3W13, NIH, Bethesda, MD 20014); Dedrick, R. L.; Matthews, H. B.; Eling, T. E.; Anderson, M. W. *Drug Metab Dispos* 5(4): 386-396; 1977.

A pharmacokinetic model was used to simulate experimental data on the distribution, metabolism, and excretion of ^{14}C -labeled 4-chloro-, 4,4'-dichloro-, 2,2',4,5,5'-pentachloro-, 2,2',4,4',5,5'-hexachlorobiphenyl (1-, 2-, 5-, and 6-CB, respectively) in male Sprague Dawley rats. The compounds were administered iv at a dose of 0.6 mg/kg. The animals were killed by cervical dislocation at times ranging from 10 min to 42 days, and the tissues analyzed. Results are described for the rapidly metabolized 1-CB and the very slowly metabolized 6-CB. Data from 1-CB indicated that $> 95\%$ of the compound in the blood was metabolized within 1 hr; by 48 hr, $> 97\%$ of the total dose had been recovered from the feces and urine. 1-CB concentrations in the fat, liver, and skin were higher than those in the blood, while muscle concentrations were lower. The concentrations in the skin, muscle and fat were mostly parent compound; traces elsewhere were of the metabolite. In contrast, 80% of 6-CB remained at 6 wk. Concentrations of 6-CB accumulated initially in the blood and gradually decreased. 6-CB concentrations in the fat, skin, liver and muscle were higher than blood concentrations. An increase in body fat by day 42 resulted in a dilution of 6-CB content in the fat and a shift of blood 6-CB to the fat. There was little difference in the fecal excretion of 1-, 2-, 5-, and 6-CB metabolites; urinary excretion exhibited a strong inverse relationship to the degree of chlorination. The agreement between the model and the experimental data is discussed. (20 refs.)

77-6817 **Dosimetry of Cigarette Smoke in Laboratory Animals.** (Eng) Pullinger, D. H. (Harrogate, Yorks., England); Houseman, T. H. *Proc Eur Soc Toxicol* 18: 265-266; 1977.

Decachlorobiphenyl (DCBP) and ^{14}C -2,4-dichlorophenoxyacetic acid (2,4-D) were used as markers of total particulate matter (TPM) uptake in female rats exposed to cigarette smoke for 3 wk. The relationship between vapor phase and TPM uptake, as a function of carbon monoxide concentration in the blood, was linear for both particulates. The advantage of 2,4-D is that it is rapidly absorbed and excreted, enabling TPM to be quantitated by scintillation counting or electron-capture gas chromatography of urine. In contrast, DCBP is retained, particularly in the respiratory tract, and it requires sacrifice of the exposed animals. (no refs.)

- 77-6818 **Two-Stage Control of Cell Proliferation Induced in Rat Liver by α -Hexachlorocyclohexane.** (Eng) Schulte-Hermann, R. (Institut für Toxikologie und Pharmakologie der Philipps Universität Marburg an der Lahn, 355 Marburg an der Lahn, W. Germany). *Cancer Res* 37(1): 166-171; 1977.

Experiments with female Wistar rats showed that dietary protein influences the induction of hepatic DNA synthesis by α -hexachlorocyclohexane (α -HCH, 150 mg/kg po by stomach tube). Stimulation of DNA synthesis by α -HCH began after a lag phase (prereplicative phase) of approx 20 hr. The initiation of DNA synthesis was suppressed by fasting or protein deprivation, but it occurred 5-8 hr after readministration of a protein-containing diet. The diurnal rhythm had no direct effect on the timing of DNA synthesis, although an increase in food intake at the onset of the dark period promoted synthesis. The results indicate that in the absence of nutrients, cells committed to DNA replication are arrested during the prereplicative phase. After protein ingestion, the cells enter the S phase almost synchronously. (37 refs.)

- 77-6819 **Experimental Study of the Carcinogenicity of Chloroprene.** (Rus) Zil'fian, V. N. (Lab. Carcinogenesis, Scientific Res. Inst. Roentgenology and Oncology, Armenian SSR Ministry Public Health, Erevan, USSR); Fichidzhian, B. S.; Garibian, D. Kh.; Pogosova, A. M. *Vopr Onkol* 23(4): 61-65; 1977.

The carcinogenicity of chloroprene (CP) was studied in male and female albino mice and rats. A rapid skin test, based on the disappearance of sebaceous glands and hair follicles upon topical application, revealed no carcinogenic activity for CP. Long-term tests of CP included topical application to mice (50% solution in benzene, 50 times), sc administration to rats (10 x 400 mg/kg or 50 x 200 mg/kg), intragastric administration to rats (50 x 200 mg/kg), and intratracheal administration to rats (5 x 200 mg/kg at 20-day intervals). None of these animals developed tumors. No tumors were found after topical application of CP (50% solution, 50 times) plus dimethylbenzanthracene (DMBA: 0.01% solution, 5 times) but DMBA alone (0.1% solution, 50 times) induced tumors in 92% of the mice. When CP was administered sc (50 x 200 mg/kg) with DMBA (1 x 0.5 mg), the tumor induction rate was 57.1%, but the same dose of DMBA alone induced tumors in 64% of the rats. The findings indicate that CP is not carcinogenic. (24 refs.)

- 77-6820 **Kepone Induction of Hepatic Mixed Function Oxidases in the Male Rat.** (Eng) Mehendale, H. M. (Dept. Pharmacology and Toxicology, Univ. Mississippi Medical Center, Jackson, MS 39216); Takanaka, A.; Desai, D.; Ho, I. K. *Life Sci* 20(6): 991-998; 1977.

The effect of decachlorooctahydro-1,3,4-metheno-2H-

cyclobuta(cd)pentalen-2-one (chlordecone, or Kepone) on the hepatic mixed function oxidase system of male Sprague-Dawley rats was investigated. The rats were fed 50, 100, or 150 ppm of the compound in the diet for 16 days for a total av consumption of 18, 34, and 46 mg, respectively. Gain in body wt was decreased to 86%, 62%, and 33% of controls at these concentrations. Liver wt of Kepone-treated animals was unaltered, but the organ was redder than controls. Amino hydroxylase activity was significantly increased at all three exposure levels, but its induction was only significant at the higher levels when it was expressed in terms of specific activity. Aliphatic hydroxylation was generally increased at all levels, as was pentobarbital hydroxylase activity. The latter was constantly higher than aniline hydroxylase activity. N-Demethylase activity, with aminopyrine as a substrate, was increased, with max induction at 50 ppm Kepone. NADPH cytochrome c reductase was significantly increased at 100 and 150 ppm cytochrome. P-450 levels were significantly increased at all concentrations, but cytochrome B, and NADPH dehydrogenase levels were unaltered. Microsomal protein content was significantly increased at 100 and 150 ppm. These findings suggest that Kepone is an efficient inducer of the hepatic mixed function oxidase system. (27 refs.)

- 77-6821 **Protective Effect of DDT and Some of Its Metabolites on the Toxicity of 7,12-Dimethylbenz(a)anthracene.** (Rus) Chemeris, G. Iu. (Lab. Carcinogenic Substances, Oncological Scientific Center, Acad. Medical Sciences USSR, USSR); Turusov, V. S. *Vopr Onkol* 23(5): 71-75; 1977.

The protective effect of dichlorodiphenyltrichloroethane (DDT), 2,2-bis(p-chlorophenyl)-1,1-dichloroethane (DDE), 2,2-bis(p-chlorophenyl)-1,1-dichloroethane, 2,2-bis(p-chlorophenyl)-1-chloroethane (DDMU), 2,2-bis(p-chlorophenyl)ethanol, 2,2-bis(p-chlorophenyl)acetic acid, and 4,4'-dichlorobenzophenone was studied in random-bred female albino rats given a single dose of 7,12-dimethylbenz(a)anthracene (DMBA: 30 mg/100 g intragastrically). The extent of protection was assessed from the 3-day survival and the degree of adrenolytic (necrotic) changes caused by DMBA. DDT, administered intragastrically in 10- or 100-mg/kg/day doses on 3 consecutive days, nearly eliminated the necrotic changes, and prevented the lethal effect of DMBA administered on day 4. Other experiments, in which DDT and its metabolites were administered in single 100-mg/kg doses 1 day before DMBA, revealed the protective action of DDE, DDT, and DDMU. The other metabolites had no appreciable effect. DDE was most protective when it was administered 2-4 or 6-8 days before DMBA. The findings indicate that DDE is a stronger inducer of liver enzymes than DDT. (16 refs.)

- 77-6822 **p,p'-DDT: Studies on Induction Mechanisms of Microsomal Enzymes in Rat Liver Systems.** (Eng) Conaway, C. C. (Dept. Entomology, Univ. Wisconsin,

Madison, WI 53706); Madhukar, B. V.; Matsumura, F. *Environ Res* 14(2): 305-321; 1977.

Induction of protein synthesis by 2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane (p,p'-DDT) in the Sprague-Dawley rat liver is shown to occur at the level of translation. This DDT-induced change is not accompanied by a marked increase in ribosomal RNA or in the rate of microsomal phosphorylation from [γ - 32 P] ATP. Actinomycin D and α -amanitin, which inhibit RNA synthesis, had no effect on the induction of cytochrome P-450. It is concluded that p,p'-DDT acts mainly on the initiation and elongation of protein synthesis at the ribosomal level. (50 refs.)

77-6823 **Some Regularities in the Abnormal Differentiation of Enzyme Activity During Blastomeres.** (Rus.) Saliamon, L. S. (No affiliation given); Ostretsova, I. B.; Senatorova, T. A. *Vestn Akad Med Nauk SSSR* (3): 14-17; 1977.

Abnormal differentiation in carcinogenesis is closely associated with disturbance of intracellular regulation. Mice inoculated with the carcinogen carbon tetrachloride showed increased α -fetoprotein levels in the serum and increased creatine kinase and alkaline phosphatase activities in the liver. These changes were less pronounced in mice subjected to hepatectomy and in rats inoculated with carbon tetrachloride. (20 refs.)

77-6824 **Alkylation of DNA and Proteins in Mice Exposed to Vinyl Chloride.** (Eng) Osterman-Golkar, S. (Wallenberg Lab., Univ. Stockholm, Lilla Frencati, S-104 05 Stockholm 50, Sweden); Hultmark, D.; Segerback, D.; Calleman, C. J.; Gothe, R.; Ehrenberg, L.; Wachmester, C. A. *Biochem Biophys Res Commun* 76(2): 259-266; 1977.

Male CBA, BALB, and ATL mice (2-3 mo old) were exposed to various doses (98-160 ppm/hr) of 14 C-labeled vinyl chloride in glass inhalation chambers for 2-10 hr, and alkylation products recovered from their Hb, testes protein, and liver DNA were quantitatively measured. Chromatographic results indicated that vinyl chloride is metabolically activated to form an alkylating agent that introduces the 2-oxoethyl group onto nucleophilic sites; alkylation by chloroethanol was negligible. The alkylation of cysteine and histidine in Hb and of guanine-7 in liver DNA varied with the strain of mice used. Considering the sensitivity of the alkylating agents to changes in nucleophilic strength, chloroethylene oxide appeared to be the main reactive metabolite. Male rodents were exposed to the alkylating intermediate, and a risk of heritable damage as well as cancer can be expected. (18 refs.)

77-6825 **Mortality Experience of Workers Exposed to Vinyl Chloride Monomer in the Manufacture of Polyvinyl Chloride in Great Britain.** (Eng) Fox, A. J. (Office Population Censuses and Surveys, St. Catherine's House, 10 Kingsway, London WC2B 6Jp, England); Collier, P. F. *Br J Ind Med* 34(1): 1-10; 1977.

The mortality incidence in 7,717 workers in the vinyl chloride industry in Great Britain was investigated. Approx 99% of these workers were traced; 12% had been exposed to constant high levels, but only 34 men had been exposed to constant high levels for > 20 yr because of the newness of the industry. The standard mortality ratio was below that expected. Four cases of liver cancer were found, one primary cancer (vs 0.71 expected), and three other liver cancers (vs 0.93 expected). Two were angiosarcomas, and the other two were carcinomas. The two workers with angiosarcoma died 8 and 21 yr after initiation of exposure to high concentrations. Other cancers vs their expected incidences were as follows: stomach, 14 vs 15.33; lung, 46 vs 51.23; brain, 2 vs 3.66; and lymphatic and hematopoietic tissues, 9 vs 9.01. The observed death rate from all cancers was 115 compared to an expected 126.77; there is no evidence that cancer at sites other than the liver was associated with exposure to vinyl chloride. Conclusions drawn from this survey must be tempered by the reservation that the full impact of the problem may not yet be in evidence. (18 refs.)

77-6826 **Dose-dependent Fate of Vinyl Chloride and Its Possible Relationship to Oncogenicity in Rats.** (Eng.) Watanabe, P. G. (Toxicology Res. Lab., Health and Environmental Res., Dow Chemical Co., Midland, MI 48640) Gehring, P. J. *Environ Health Perspect* 17: 145-152; 1977.

Studies were made of the disposition of radioactivity from different doses of po administered or inhaled 14 C-vinyl chloride (VC) in excreta, expired air, and body tissues of treated rats and of nonprotein sulfhydryl levels in the livers of treated rats. The disposition of VC was found to be a function of dose, particularly after administration po. The percentages of administered VC radioactivity in rats treated po with 0.05 mg/kg VC were 1.4%, 9.0%, 68.3%, 2.4%, and 10.1% in exhaled VC, exhaled carbon dioxide, urine, feces, and carcass, respectively; following 100 mg/kg VC, the corresponding values were 66.6%, 2.5%, 10.8%, 0.5%, and 1.8%; following inhalation of 10 ppm VC, the corresponding values were 1.6%, 12.1%, 68%, 4.5%, and 13.9%; following inhalation of 1,000 ppm VC, the corresponding values were 12.3%, 12.3%, 56.3%, 4.2%, and 14.5%. Exposure to 150, 250, 1,000 or 2,000 ppm VC caused a progressive depression of the hepatic nonprotein sulfhydryl content; exposure to 50 ppm VC for 7 hr produced a small, inconsistent depression; no depression was observed in rats exposed to 10 ppm. These results indicate that statistical projections of data from rats exposed to high doses of VC are

not valid for predicting effects of low-level exposure, because the metabolism of VC at different dose levels is not the same. (13 refs.)

- 77-6827 **Vinyl Chloride Cytogenetics.** (Eng.) Picciano, D. J. (Occupational Health and Medical Res., Texas Div., Dow Chemical U.S.A., Freeport, TX 77541); Flake, R. E.; Gay, P. C.; Kilian, D. J. *J Occup Med* 19(8): 527-530; 1977.

A cytogenetic evaluation was made of 209 workers who had been exposed to vinyl chloride at the Texas Division of Dow Chemical USA. The workers were employed for periods ranging from 1 to 332 mo (av 48.3 mo). Blood samples were taken, and the lymphocyte chromosomes were evaluated. There were no major differences between the workers and controls with respect to chromatid breaks, chromosome breaks, rings, dicentric, exchange figures, and the proportion of abnormal cells. Because of these negative findings and conflicting results by others, cytogenetic aberrations due to vinyl chloride are believed to be related to the length and level of exposure. Risk of adverse effects can be controlled by minimal-exposure environments. (31 refs.)

- 77-6828 **In Vitro Metabolic Activation of Ethidium Bromide and Other Phenanthridinium Compounds: Mutagenic Activity in *Salmonella typhimurium*.** (Eng.) MacGregor, J. T. (Western Regional Res. Lab., Agricultural Res. Service, US Dept. Agriculture, Berkeley, CA 94710) Johnson, I. J. *Mutat Res* 48(1): 103-108; 1977.

The mutagenic effect of four phenanthridinium compounds (150C47, ethidium bromide, carbidium, and prothidium) was investigated in *Salmonella typhimurium* strains TA98, TA1538, TA1537, TA100, and TA1535. In the presence of a rat liver metabolizing-enzyme system, all four compounds were activated to potent mutagens in the frameshift tester strains TA98 and TA1538. Compound 150C47 was more mutagenic than ethidium and, therefore, may be a more effective molecular probe. (24 refs.)

- 77-6829 **Chloramphenicol Damages Bacterial DNA.** (Eng.) Jackson, S. F. (Dept. Biochemistry, McMaster Univ., Hamilton, Ontario, Canada L8S 4J9); Wentzell, B. R.; McCalla, D. R.; Freeman, K. B. *Biochem Biophys Res Commun* 78(1): 151-157; 1977.

The Ames test was used to determine the mutagenicity of L(+)-threo-chloramphenicol (L(+))CAP and its isomer D(-)CAP on *Salmonella typhimurium* strains TA100, TA98, TA1535, and TA1976 and on *Escherichia coli* B/r. L(+))CAP induced His⁺ revertants in strains TA100 and TA1535 but not TA98 at concentrations ranging from 0.6 to

5 mM. With the modified fluctuation test, the mutagenicity of L(+))CAP could be detected at concentrations as low as 0.5 millim. The effect was dose-related up to concentrations of 200 μ M. The L(+)-p-methylsulfonyl and L(+)-p-methylthio analogs of L(+))CAP failed to induce revertants in TA100, TA1535, or TA98. D(-)CAP did not produce any revertants, but mutagenicity could have been masked by its toxicity at levels as low as 0.02 millim. The L(+) isomer caused single-strand breaks in the DNA of *E. coli* and *S. typhimurium* TA1535, TA100 and TA1976. D(-)CAP was somewhat less effective, and it did not produce breaks in TA1535 or TA100. (22 refs.)

- 77-6830 **Airborne Mutagens Bioassayed in *Salmonella typhimurium*.** (Eng.) Talcott, R. (Dept. Biomedical and Environmental Health Sciences, Sch. Public Health, Berkeley, CA 94720); Wei, E. *J Natl Cancer Inst* 58(2): 449-451; 1977.

Particulate airborne pollutants were collected in March 1962 in Buffalo, NY, at a station located downwind from a steel mill, and the samples were extracted with acetone and tested for mutagenicity in the *Salmonella typhimurium* test system. These results were then compared with those of fresh samples of airborne particulate matter collected in Berkeley, CA. With the Buffalo sample, a frameshift mutation was observed in *S. typhimurium* strains TA100, TA98, and TA1537. Max expression occurred in the presence of liver microsomes from rats given Aroclor 1254. This activity was 50% inhibited by the addition of 7,8-benzoflavone (100 μ g/plate) and reduced 90% by the addition of microsomes from control rats. Therefore, most of the mutagenicity of the Buffalo samples was due to the presence of polycyclic aromatic hydrocarbons (PAH), since PAH are also activated by Aroclor 1254-inducible aryl hydrocarbon hydroxylase, an enzyme specifically inhibited by benzo-flavone. In addition, the Buffalo sample contained direct-acting mutagens. In strains TA98 and TA1537, 20%-25% of the total mutagenic activity was expressed in the absence of microsomes. Only direct-acting mutagens were found in the Berkeley samples; therefore, the direct-acting mutagens in the Buffalo sample were not merely artifacts of storage. Since polluted air may contain two classes of mutagens and/or carcinogens, measurements of PAH or benzo(a)-pyrene alone may not adequately reflect the total carcinogenic potential. (17 refs.)

- 77-6831 **Activation of a Procarcinogen to a Mutagen by Cell-free Extracts of Anaerobic Bacteria.** (Eng.) McCoy, E. C. (Dept. Microbiology, N.Y. Medical Coll., Valhalla, NY 10595); Speck, W. T.; Rosenkranz, H. S. *Mutat Res* 46: 261-264; 1977.

These studies were made to determine whether anaerobic bacteria could be coupled to the mutagenicity assay in a manner similar to that used for liver microsomes. Mutagenicity

esting was accomplished by the Ames method. Cell-free extracts prepared from the major gastrointestinal flora (*Clostridium perfringens* and *Bacteroides fragilis*) were both active in metabolizing a procarcinogen (2-aminofluorene) to a substance mutagenic for *Salmonella typhimurium*. No activity was shown when the anaerobic bacteria extracts were omitted, heated to 80 C, or when pronase was put into the plate assay. Minimal activity resulted from aerobic incubation conditions. After 1-4 wk, the assays showed reduced activity. The *Salmonella* mutagenicity assay can be used to study the role of anaerobic flora in the activation of chemical carcinogens. (24 refs.)

77-6832 The Action of N-Hydroxy-2-acetylaminofluorene on the Synthesis of Ribosomal and Poly(A)-RNA in Normal and Regenerating Liver. (Eng) Glazer, R. I. (Dept. Pharmacology, Emory Univ., Atlanta, GA 30322). *Biochim Biophys Acta* 475(3): 492-500; 1977.

Normal and partially hepatectomized male Sprague-Dawley rats (150-170 g) were inoculated ip with N-hydroxy-2-acetylaminofluorene (N-OH-AAF) 18 hr after partial hepatectomy. To label polysomal RNA, 500 μ Ci/kg of 5-³H-uracil acid diluted in 0.9% NaCl was injected ip and allowed to incorporate for 30 or 90 min. The effects of N-OH-AAF on the poly(A)RNA and ribosomal RNA (rRNA) fractions of polysomal RNA were analyzed using poly(U)-Sepharose chromatography. A dose of 20 mg/kg N-OH-AAF preferentially impaired rRNA synthesis, whereas 40 mg/kg equally inhibited rRNA and poly(A)-RNA. Thus, in contrast to rRNA, poly(A)-RNA appears to be less stoichiometric and remains unperturbed by extensive nuclear inhibition. Measurements of the poly(A) content of poly(A)-RNA using *Escherichia coli* DNA polymerase I showed that N-OH-AAF did not significantly affect the size of the poly(A) sequences in polysomal RNA, suggesting that polyadenylation per se is not involved in the action of N-OH-AAF. (27 refs.)

77-6833 N-Hydroxylase Activity: A New Method for Its Evaluation and Biological Implications. (Eng) Mercier, M. J. (Lab. Biotoxicology, Unite de Chimie Medicale, Toxicologie et Bromatologie, Univ. Louvain Sch. Pharmacy, Brussels, Belgium); Razzouk, C.; Roberfroid, M. In: *Clinical Toxicology. Proceedings of the Meeting held at Edinburgh, June 1976*. Duncan, W. A.; Leonard, B. J.; eds. (Amsterdam: Excerpta Medica); vol 18, pp. 329-331; 1977.

A method for the isolation and estimation of N-hydroxy-2-acetylaminofluorene (N-OH-2AAF) using gas chromatography and electron capture detection is presented. R Strain male Wistar rats were treated with either 75 mg/kg sodium phenobarbital (PB) ip 48 and 24 hr before sacrifice, 40 mg/kg methylcholanthrene (MC) ip 24 hr before sacrifice, or 10

mg/kg 2AAF or 4AAF po 24 hr before sacrifice. Upon sacrifice, microsomes were prepared from excised livers, and N-hydroxylation was initiated by adding 0.25 ml of microsomal suspension and 0.25-3 μ M 2AAF to a preincubated NADPH-generating system. Addition of 50 nanograms of N-hydroxy-4-acetylaminobiphenyl (N-OH-4AABP) served as an internal standard. After treatment of the incubation mixture with HCl, the reaction products were identified as the corresponding N-chloro-arylamines. Treatment with trifluoroacetic anhydride gave rise to the N-chloro-N-trifluoro derivatives of N-OH-2AAF and N-OH-4AABP. Chromatography allowed the measurement of a little as 50 picog N-OH-2AAF/ml incubation mixture. A concentration of 3 μ M 2AAF was sufficient to saturate the N-hydroxylase reaction; the time course was linear, however, up to 20 min and up to a protein concentration of 0.2 mg. The effect of the previously described pretreatments of the Michaelis-Menton kinetics of the reaction were then investigated. Only 2AAF and MC significantly modified the enzyme by decreasing its affinity for the substrate. 4AAF did not produce any effect. It is suggested that a correlation exists between the carcinogenicity of a compound and its ability to modify the hydroxylase. (4 refs.)

77-6834 Mammary Carcinogenesis in the Rat by Topical Application of Fluorenylhydroxamic Acids and Their Acetates. (Eng) Malejka-Giganti, D. (Lab. Cancer Res., Veterans Admin. Hosp., Minneapolis, MN 55417); Rydell, R. E.; Gutmann, H. R. *Cancer Res* 37(1): 111-117; 1977.

The carcinogenicity of a single application of 0.02 millim N-fluorenylacetamide (2-FAA), N-hydroxy-2-FAA, N-acetoxy-2-FAA, 3-FAA, N-hydroxy-3-FAA, or N-acetoxy-3-FAA to the mammary glands of female Sprague-Dawley rats was investigated. The total tumor incidence, number of rats with tumors at the application site, and the number of rats with tumors at distant sites for the respective compounds were: 3/18, 2, and 1; 13/19, 9, and 6; 5/18, 4, and 2; 2/18, 2, and 0; 15/18, 15, and 6; and 18/18, 18, and 4. The mean latent period of the malignant tumors resulting from the fluorenylamides was twice as long as that of the tumors due to the hydroxamic acids. Further experiments suggested that N-hydroxylation of the arylamines was a prerequisite for mammary carcinogenesis; however, since there was no evidence for N-hydroxylation of 2-FAA or 3-FAA in the mammary glands, it was concluded that this activation occurred in the liver. Carcinogenesis in ovariectomized animals was investigated following a single application of 0.02 millim N-hydroxy-2-FAA and N-hydroxy-3-FAA to the mammary glands. These rats did not develop tumors; administration of estradiol (total dose, 0.45 mg im) and the fluorenylhydroxamic acids did not improve tumor yield. These results indicate that induction of mammary tumors by fluorenylhydroxamic acids is under hormonal control. (46 refs.)

- 77-6835 Effect of N-2-Acetylaminofluorene Modification on the Structure and Template Activity of DNA and Reconstituted Chromatin.** (Eng) Yamasaki, H. (Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY 10032); Leffler, S.; Weinstein, I. B. *Cancer Res* 37(3): 684-691; 1977.

The in vitro modification of native duck reticulocyte DNA by ^{14}C -N-acetoxy-2-acetylaminofluorene (N-OH-AAF) was studied in relation to alterations in DNA secondary structure, ability to reconstitute nucleosome structures in chromatin, and template activity for in vitro transcription. In contrast to control native DNA, the carcinogen-modified DNA was susceptible to partial digestion by the single-strand-specific endonuclease S_1 . Depending on the particular conditions, for every ^{14}C -N-OH-AAF residue released, about 5-35 DNA base pairs were also released during S_1 nuclease digestion. Chromatin was reconstituted in vitro utilizing ^{14}C -N-2-acetylaminofluorene (AAF)-modified DNA and unmodified chromatin-associated proteins. This reconstituted chromatin showed the same kinetics and extent of digestion by staphylococcal nuclease and similar nucleosome profiles on sucrose gradient density centrifugation as those obtained with native chromatin or chromatin reconstituted with unmodified DNA. However, the carcinogen-modified DNA and the chromatin reconstituted from this DNA showed marked reductions in their abilities to serve as templates for transcription with *Escherichia coli* RNA polymerase. These results suggest that the covalent binding of AAF to DNA produces localized regions of denaturation in the DNA and that this is associated with a marked impairment in template activity during transcription. This modification, however, does not grossly affect the ability of the DNA to interact with chromosomal proteins to form apparently normal nucleosome structures. (39 refs.)

- 77-6836 Absorption and Protein Binding of N-2-Fluorenylacetamide and Its Metabolites in the Bladder of the Rabbit.** (Eng) Hopp, M. L. (Dept. Pathology, Northwestern Univ. Medical Sch., 303 E. Chicago Ave., Chicago, IL 60611); Matsumoto, M.; Lee, C.; Oyasu, R. *J Natl Cancer Inst* 58(2): 281-285; 1977.

The absorption of N-2-acetylaminofluorene (AAF) and its metabolites, N-hydroxy-2-acetylaminofluorene (N-OH-AAF) and the N-O-glucuronide of AAF (N-OGI-AAF), by the rabbit (male New Zealand White) bladder mucosa, as well as binding to the protein and RNA of bladder mucosa, were measured in vivo and in vitro. Mucosal pieces were incubated for 3 hr in medium containing labeled carcinogen, and the radioactivity bound to protein and RNA and absorbed by the entire tissue was analyzed. The fluorene nucleus of both AAF and N-OH-AAF bound equally with cellular proteins, but N-OGI-AAF binding was lower. In the presence of an excess of β -glucuronidase, however, N-OGI-AAF showed binding equivalent to its metabolic precursor. No consistent repeat-

able radioactivity levels could be associated with RNA regardless of the carcinogen used as a substrate. Radioactive carcinogens suspended in urine were instilled into the bladder lumen for 3 hr in vivo. Transmural absorption of AAF and N-OH-AAF was substantial (90%), but N-OGI-AAF was absorbed less (55%). Renal excretion during this period varied from 18% to 52% of the instilled radioactivity. The in vivo and in vitro metabolism of N-OH-AAF and N-OGI-AAF was such that the acetyl group was not included in the final protein-carcinogen complex in what appeared to be an enzyme reaction. It is speculated that a form of deacetylating activity might be present in the bladder and a subsequent nitroso metabolite may account for reactions with the bladder mucosal proteins. (34 refs.)

- 77-6837 Enhancing Effects of Phenobarbitone and Butylated Hydroxytoluene on Acetylaminofluorene-induced Hepatic Tumorigenesis in the Rat.** (Eng.) Peraino, C. (Div. Biological and Medical Research, Argonne Natl. Lab., Argonne, IL 60439); Fry, R. J.; Staudt, E.; Christopher, J. P. *Food Cosmet Toxicol* 15(2): 93-95; 1977.

A comparison was made of the ability of dietary phenobarbitone (PBT, 0.05% po for 7 days) and dietary butylated hydroxytoluene (BHT, 0.5% po for 7 days) to enhance hepatic tumorigenesis in 22-day-old male Sprague-Dawley rats that had been previously fed 2-acetylaminofluorene (AAF, 0.02% po for 18 days). Tumors appeared in 6/92 rats fed AAF alone, but 58/93 rats fed AAF plus PBT and 24/40 rats fed AAF plus BHT developed tumors. PBT injections (83 mg/kg ip, daily x 5) stimulated liver enlargement and a transient four-fold increase in DNA synthesis. BHT injections (500 mg/kg ip, daily x 5) produced a less pronounced liver enlargement after a delay of 1 day and did not stimulate DNA synthesis. These results suggest that the dissimilar tumorigenic-enhancing abilities of PBT and BHT may result from differences in their effects on biochemical processes related to tumor growth. (14 refs.)

- 77-6838 Use of Guinea Pigs to Study the Blastomogenic Activity of Some Endogenous Substances.** (Rus.) Khrustalev, S. A. (Dept. Experimental Animals, Oncological Scientific Center, Acad. Medical Sciences USSR, Moscow, USSR); Khar'kovskaya, N. A.; Vasil'eva, N. N. *Biull Eksp Biol Med* 34(8): 200-202; 1977.

The carcinogenic activities of two endogenous metabolites, tryptophan, 3-indolylacrylic acid (IAA) and aminoacetophenone (AAP), were studied in 2-mo-old male and female mongrel guinea pigs. Both substances were administered sc in doses of 30-50 mg (in 0.5 ml distilled water) at 2- to 3-day intervals over 3-4 mo. Total doses were 120 mg for IAA and 740 mg for AAP. The animals were observed until death. Tumor incidence was similar in the experimen-

groups (3/30 for IAA and 3/20 for AAP) and in the controls (7/40). However, tumor latency was considerably shorter in the experimental groups (2.5 yr for IAA and 3.5 yr for AAP) than in the controls (54 mo), and the average age of the tumor-bearing animals was 47 mo in the experimental groups and 55 mo in the controls. The tumors that occurred were different histologically. Tumors found in the controls included three adenomas, one carcinoma of the adrenal cortex and one ovarian dermoid cyst. Tumors found in the IAA group included one insulinoma of the pancreas and one angiosarcoma of the mesentery. Two ovarian leiomyomas and 1 angiosarcoma of sc tissue were found in the AAP group. These tumors occur spontaneously very rarely, if at all, in guinea pigs. The findings indicate the carcinogenicity of both tryptophan metabolites and the possibility of using guinea pigs for the carcinogenicity testing of weak endogenous carcinogens. (15 refs.)

77-6839 The Role of Dog Bladder Mucosa in the N-Oxidation of Arylamines. (Eng.) Brill, E. (Dept. Pharmacology, Univ. Miami Sch. Medicine, Miami, FL 33152). *Res Commun Chem Pathol Pharmacol* 16(1): 73-84; 1977.

The in vitro metabolic N-oxidation of 1-naphthylamine, 2-naphthylamine, 4-biphenylamine, 2-fluorenylamine, and 3-dibenzofuranyllamine was investigated in intact dog bladder, whole intact bladder mucosa, and microsomes prepared from this tissue. Two techniques were used to detect N-oxidation: ferrihemoglobin formation in dog RBC added to the incubation mixture and gas-liquid chromatography of samples of reaction solution removed at 5, 10, and 30 min. Very low levels of metabolic N-oxidation of the test amines were detected in these tissue preparations using ferrihemoglobin formation. No N-oxidation was observed using gas-liquid chromatography. Neither method detected N-oxidation in the microsomal preparations with or without an added NADPH-generating system. Although the methods used to prepare and store the microsomes resulted in active preparations from dog liver, it appears that the isolation method used is too harsh for dog bladder mucosa and/or that the bladder microsomes lose enzymatic activity on storage. (18 refs.)

77-6840 Carcinogen Control in the Urine of Dogs During Bladder Carcinogenesis. (Eng.) Gericke, D. (Hoeschst AG, D-6230 Frankfurt/Main-80, W. Germany); Grottsch, H.; Harzmann, R.; Bichler, K. H. *Naturwissenschaften* 64(7): 392-393; 1977.

The Ames test, using various *Salmonella typhimurium* strains, was used to supervise the urinary excretion of carcinogens after sc application in beagle dogs. Sixteen females were given bladder stones transurethrally with fluid Paladur or Technovit 4071. Twelve of these dogs were divided into three groups of four dogs each and treated twice a week with

2-formylamine-4-(5-nitro-2-furyl)-thiazol (FANFT: 25 mg/kg), o-aminodiphenyl (OADP: 30 mg/kg), or with FANFT (20 mg/kg) + OADP (20 mg/kg). Four dogs developed bladder stones only. *S. typhimurium* strain TA100 was employed with and without enzymatic activation (S-9 mix). TA100 reacted only with the dogs that were treated with FANFT or with FANFT + OADP. The urine of the other dogs showed negative results. The S-9 mix was not found to be necessary. TA98, TA1535, and TA1537 gave negative results. Thus, after sc application, FANFT appears in the urine as a carcinogen that causes mutations with TA100, but OADP does not reach the bladder in such a form. The Ames test has made it possible to show bladder carcinogens in the urine of dogs. (6 refs.)

77-6841 A Long-term Study of Reversible and Progressive Urinary Bladder Cancer Lesions in Rats Fed N-[4-(5-Nitro-2-furyl)-2-thiazolyl]formamide. (Eng.) Jacobs, J. B. (Dept. Pathology, St. Vincent Hosp., Worcester, MA 01604); Arai, M.; Cohen, S. M.; Friedell, G. H. *Cancer Res* 37(8, part 2): 2817-2821; 1977.

The long-term changes in Fischer rat urinary bladder following administration of N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) are reported. Eight groups of rats, 40/group, were fed FANFT in the diet, 0.2% by wt, for 2, 4, 6, 8, 10, 12, 14, or 20 wk, respectively. The rats were maintained on a carcinogen-free diet until the 84th wk. Rats fed FANFT for periods up to 6 wk developed moderate epithelial hyperplasia that regressed when the rats were placed on the control diet. Rats fed FANFT for 8 to 10 wk developed moderate to marked hyperplasia with focal nodular or papillary lesions that were not reversible. All rats fed FANFT for 12, 14, and 20 wk had transitional cell tumors associated with marked hyperplasia of the mucosa. The epithelial changes induced after 6 and 8 wk on the diet were visible by scanning electron microscopy. Pleomorphic microvilli indicated irreversible and potentially malignant epithelial changes. (11 refs.)

77-6842 Neoplastic Transformation Induced by Furfurylamine and Nitromethylfuran of Embryonic Hamster Cells in Tissue Culture. (Eng.) Nishi, Y. (Section Cell Biology and Cytogenetics, Biological Res. Center, Japan Tobacco and Salt Public Corporation, Hatano, Kanagawa 257, Japan); Taketomi, M.; Inui, N. *Int J Cancer* 20(4): 607-615; 1977.

Secondary cultures of Syrian hamster embryo fibroblasts were tested for transformation and neoplastic properties after exposure in vitro to furfurylamine [2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, or AF-2] and other nitrofurans. Typical morphological transformation was seen in 5/6 cultures between 30 and 186 days following treatment with $5-10 \times 10^6$

M AF-2 for 24 hr. Transformation occurred in only 1/4 cultures 145 days after treatment for 6 hr with AF-2. Treatment with $5 \cdot 10 \times 10^{-6}$ M 5-nitro-2-methylfuran (NMF) for 24 hr also induced transformation after 50 and 118 days in two cultures. In contrast, untreated cultures and cultures treated with $5 \cdot 10 \times 10^{-6}$ M 4-(5-nitro-2-furyl)thiazole (NFT) for 24 hr were not transformed within 200 days. Three of six lines transformed by AF-2 and both lines transformed by NMF also became tumorigenic 7-24 days after morphologic transformation. The other three transformed lines produced nodules that regressed within a few weeks of transplantation. Untreated and treated nontransformed lines did not produce tumors during a 6-mo observation period. The tumors were fibrosarcomas. The ability to form colonies in soft agar was acquired by only one tumorigenic lines. (37 refs.)

- 77-6843 Content of 3-HAA Antigens and Corresponding Antibodies in Mice During Early Stages of Hepatocarcinogenesis.** (Rus) Korosteleva, T. A. (Lab. Immunology Carcinogenesis, N. N. Petrov Scientific Res. Cancer Inst., Leningrad, USSR); Shvaidetsky, I. I. *Vopr Onkol* 23(6): 73-78; 1977.

The presence and excretion of 3-hydroxyanthranilic acid (3-HAA) antigens and antibodies in the tissues of C3HA mice were determined during the early stages of o-aminoazotoluene (OAT)-induced carcinogenesis. The mice were fed OAT (2 mg/mouse/day) for 4, 15, 30, 45, 60, and 100 days. The animals were then sacrificed, and 3-HAA antigens and their antibodies in the blood serum, blood clots, urine, liver, lungs, kidneys, and spleen were assessed by immune rabbit sera against 3-HAA azoproteins of horse sera and by heterologous synthetic 3-HAA azoproteins. The concentration of 3-HAA antigen in the blood clots and liver of mice that received OAT for 4 days was 2.08 and 7.50 μ g, respectively. Further administration of the carcinogen resulted in an elevation of 3-HAA antigens in the liver, blood clots, and sera (none could be detected in the kidneys, lung, and spleen). From day 45 of OAT administration to the end of the experiment, the antigen concentration decreased. This decrease was correlated with the appearance of antibodies against 3-HAA azoproteins, and it is probably due to a carcinogen-induced immune response essential for carcinogen-antigen binding. (8 refs.)

- 77-6844 Transplacental Influence of o-Aminoazotoluene (OAAT) on Organ Cultures of the Embryonal Liver of C57BL and CBA Mice.** (Rus) Popova, N. V. (Oncology Res. Center, Acad. Medical Sciences USSR, Moscow, USSR). *Biull Eksp Biol Med* 83(6): 732-734; 1977.

The transplacental effect of o-aminoazotoluene (OAAT) on the growth and viability of mouse embryo liver cultures was studied in C57BL (low-carcinoma line) and CBA (high-

hepatoma line) mice. Pregnant mice received OAAT (4 mg/day \times 3 for C57BL mice, 4 or 8 mg/day \times 3 for CBA mice, po) starting on day 16 of pregnancy. They were sacrificed 3-4 days later, and the embryonal liver cultures were prepared. When administered in a total dose of 12 mg to C57BL mice, OAAT stimulated the growth of the liver cultures and increased their survival rate. On the 31st day of culture, the survival rate was 83% vs 46.1% in control cultures. For CBA liver cultures, the survival rate on day 31 of culture was 36.3% in control cultures and 41.7% after the administration of 12 mg OAAT; after the administration of 24 mg, however, the rate was 16.4% on day 4 and 43% on day 22. Thus, the high dose of OAAT, which also suppressed the growth of the culture, had a marked initial toxic effect followed by a growth-stimulating effect. The in vitro findings were corroborated by the in vivo results: no live offspring were obtained from 45 CBA mothers treated with 24 mg of OAAT during pregnancy, but all offspring born to 50 mothers treated with 12 mg of OAAT during pregnancy were alive. (8 refs.)

- 77-6845 Changes in Peroxisomes in Preneoplastic Liver of Rats Induced by 3'-Methyl-4-dimethylaminoazobenzene.** (Eng) Itabashi, M. (Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Cho-ku, Tokyo 104, Japan); Mochizuki, Y.; Tsukada, H. *Cancer Res* 37(4): 1035-1043; 1977.

Hyperplastic liver lesions in Wistar rats fed 0.06% 3'-methyl-4-dimethylaminoazobenzene were studied ultrastructurally and histochemically. The 3,3'-diaminobenzidine reaction was used to demonstrate catalase activity and thus variations in the number of peroxisomes. Hyperplastic lesions (hyperplastic foci, areas, and nodules) appeared at the 10th week of carcinogen feeding and advanced to further stages. Most of the foci and some of the areas showed very low catalase activity and, correspondingly, a small number of peroxisomes. When administered for 2 wk prior to sacrifice, ethyl- α -p-chlorophenoxyisobutyrate (CPIB) induced an increase in peroxisomes and catalase activity. The progression of hyperplastic foci to hyperplastic areas and/or nodules paralleled the proliferation and maturation of hepatocytes. Maturation was characterized by an increase in catalase levels and peroxisomes and by an enhanced response to CPIB. However, there was a small proportion of lesions in which all or some cells did not mature. It is suggested that these cells, which appeared to be permanently altered, are the precursors of hepatomas. (40 refs.)

- 77-6846 Mitochondrial Membrane-linked Reactions in Carcinogenesis: Change in Stereoselective Uncoupling of Oxidative Phosphorylation by Aliphatic Dicarboxyls and in the Arrhenius Plot of NADH-Indophenol Reductase.** (Eng) Bryant, G. M. (Seamen's Memorial Res. Lab., U.S. Public Health Service Hosp., 210 State St., New Orleans, LA 70118); Argus, M. F.; Arcos, J. C. *Gann* 68(1): 89-98; 1977.

The effects of diacetyl, acetylacetone, and acetylacetone on the respiratory parameters of normal male Sprague-Dawley rat mitochondria and rats fed 0.06% of the dye 3'-methyl-(dimethylamino)-azobenzene (3'-Me-DAB) for up to 8 wk were investigated. Diacetyl uncoupled oxidative phosphorylation in normal rat liver mitochondria, but acetylacetone and acetylacetone were increasingly less effective, in that order. Preincubation of diacetyl with the vicinal dithiol dithiothreitol reversed these effects, suggesting that diacetyl reacts with the -SH groups of dithiothreitol. Diacetyl can also react with the NH₂ groups of amino acids and effect oxidative phosphorylation. Diacetyl totally abolished respiratory control with substrates in which oxidation involves the ADH-CoQ segment, but it only partially abolished the control with succinate, which bypasses this segment. Diacetyl also uncoupled oxidative phosphorylation in liver mitochondria from rats fed 3'-Me-DAB; the mitochondria were most resistant to this uncoupling during the time when the respiratory control index was at the dye-induced minimum. This time period, which is at 3-4 wk of dye administration, represents the cumulative dose for the tumorigenesis threshold. Discontinuities in the Arrhenius plot of the mitochondrial membrane-localized NADH-indophenol reductase appear at this threshold, return to the control state by 8 wk, and reappear in the plot of the enzyme from tumor mitochondria. These phenomena suggest sequential membrane phase transitions in the mitochondria during azo dye carcinogenesis. (54 refs.)

77-6847 **Tumour-specific Complement-dependent Serum Cytotoxicity Against a Chemically Induced Rat Hepatoma.** (Eng) Price, M. R. (Cancer Res. Campaign Labs., Univ. Nottingham, Univ. Park, Nottingham NG7 2RD, England); Baldwin, R. W. *Int J Cancer* 20(2): 284-291; 1977.

Short term ⁵¹Cr-release assay was used to detect complement-dependent cytotoxic antibodies in the sera of rats sensitized to antigens from 4-dimethylaminoazobenzene-induced tumors (D23, D30, D192, and D202) in W/Not rats. Normal rat serum (NRS), in the presence or absence of complement, did not induce a cytotoxic response against cells from hepatomas D23, D192, and D202; tumor-bearer serum (TBS) from rats bearing ip implants of D23 gave cytotoxic values of 6.4% and 26.0% in the presence of complement when tested against D23 targets. A 2-hr incubation was used. This cytotoxicity was max at the terminal stage of tumor growth, and it was not detected in sera from donors bearing sc tumor grafts. Sephadex G200 fractionation of the serum revealed that the 19S fraction was the only one to show this toxicity. The NRS 19S fraction and the D23 ip TBS 19S fraction were slightly protective toward the release of ⁵¹Cr in the absence of active complement. These findings are discussed in relation to the development of humoral responses in the tumor-bearing host. (9 refs.)

77-6848 **Induction of Hepatomas Secreting Large Amounts of Alpha-Fetoprotein.** (Eng.) Smith, C. J. (Dept. Medicine, Univ. Vermont Coll. Medicine, Burlington, VT 05401); Kelleher, P. C. *Cancer Lett* 3(1-2): 53-57; 1977.

Fifty-nine of 69 Fischer rats fed 0.06% 3'-methyl-4-dimethylaminoazobenzene continuously developed palpable hepatomas that secreted large amounts of α -fetoprotein (AFP). Serum AFP concentrations in the 59 hepatoma-bearing rats ranged from 92 to 3,269 μ g/ml; (mean, 972 μ g/ml; median, 830 μ g/ml) at the time of sacrifice. Every primary tumor was established as an in vivo transplantable line; only those 39 lines that consistently give serum AFP concentrations \geq 300 μ g/ml are being maintained. (16 refs.)

77-6849 **Chromosome Banding Patterns of Two Transplantable Pituitary Tumors Induced in Rats by 2,4,6-Trimethylaniline.** (Eng) Kovi, J. (Dept. Pathology, Howard Univ. Coll. Medicine, Washington, DC 20059); Morris, H. P.; Kovi, E. *J Natl Cancer Inst* 58(2): 377-381; 1977.

The chromosome banding patterns of the transplantable pituitary tumors 7315a and 7315i, induced in rats by 2,4,6-trimethylaniline (2,4,6-TMA), were analyzed by Giemsa-banding techniques. The inactive 7315i line evolved from the active 7315a line in one of the early transfers. The chromosome patterns of the transplantable rat hepatoma 7316A, which was also induced by 2,4,6-TMA, were analyzed for comparison. Line 7315a had a pseudotriploid complement with 63 chromosomes, but line 7315i was hypodiploid with a dominant stemline of 36 chromosomes. The stemline of hepatoma 7316A was in the hypotetraploid region. Giemsa banding demonstrated that all chromosomes of the normal rat complement were present in both pituitary tumors. There were four abnormal chromosomes in line 7315a and three in line 7315i. Both contained a single minute chromosome and a common marker, a deleted chromosome 1. This common marker chromosome could not be detected in the hepatoma. Although the stemline karyotype of the hepatoma contained seven different markers, none was identical to the abnormal chromosomes of the pituitary tumor lines. The abnormal karyotypes of lines 7315a and 7315i may reflect the multisecretory activities of these neoplastic pituitary cells. However, the chromosomal localization of the secretory defect awaits detailed genetic mapping of the rat chromosomes. (22 refs.)

77-6850 **Correlation Between Sister Chromatid Exchanges (SCE) and DNA Damage Studied in Cultured Mouse Fibroblasts Exposed to N-Diazoacetyl glycine Amide (DGA) (Meeting Abstract).** (Eng.) Raffetto, G. (Regional Center for Cancer Res., Genoa, Italy); Bolognesi, C.; Parodi, S.; Brambilla, G.;

Santi, L. In: *Fourth Meeting of the European Association for Cancer Research, 13-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 65; 1977. (no refs.)

77-6851 Mutagen-Nucleic Acid Intercalative Binding: Structure of a 9-Aminoacridine:5-Iodocytidylyl(3'-5')guanosine Crystalline Complex. (Eng) Sakore, T. D. (Dept. Chemistry, Indian Inst. Technology, Bombay, India); Jain, S. C.; Tsai, C. C.; Sobell, H. M. *Proc Natl Acad Sci USA* 74(1): 188-192; 1977.

9-Aminoacridine forms a crystalline complex with the dinucleoside monophosphate 5-iodocytidylyl(3'-5')guanosine. X-ray crystallography showed that this drug binds to miniature Watson-Crick double helical structures by two intercalative modes. The first of these involves a pseudosymmetric stacking interaction between 9-aminoacridine molecules and guanosine-cytosine base pairs. The second configuration is an asymmetric interaction largely governed by stacking forces between acridine and guanine rings. The first configuration may be used by 9-aminoacridine when it intercalates into DNA and the second may play an important role in the mechanism of frameshift mutagenesis. (26 refs.)

77-6852 Behavior of Benzidine and Other Aromatic Amines in Aerobic Wastewater Treatment. (Eng) Baird, R. (County Sanitation Districts Los Angeles County, Whittier, CA); Carmona, L.; Jenkins, R. L. *J Water Pollut Control Fed* 49(7): 1609-1615; 1977.

Activated sludge samples taken from two treatment facilities were dosed to contain 1-, 10-, 20-, 40-, 100-, 250-, or 500-mg/liter concentrations of the carcinogen benzidine or 20 mg/liter of other aromatic amines found in industrial wastes. Using conventional Warburg bioassay techniques, benzidine, o-tolidine, bianisidine, tetramethylbenzidine, analine, and dimethylaniline showed inhibitory effects on the oxygen uptake of the sludge. Analysis by gas-liquid chromatography indicated that most amines showed significant depletion, even when highly toxic, after exposure to the sludge for 6 hr. However, N,N-substituted amines were not depleted much and remained quite toxic. For the monoaromatic amines, an unsubstituted position ortho- or para- to the -NH₂ appeared to be required for electrophilic attack. During the Warburg treatment of benzidine, none of the suspected carcinogenic oxidation products persisted. Metabolic intermediates appear to be responsible for the toxicity as well as carcinogenicity of the amines. (17 refs.)

77-6853 Risk of Bladder Tumors among Benzidine Workers and Their Serum Properdin Levels. (Eng) Horton, A. W. (Section Chemical Biology and Oncology,

Dept. Public Health and Preventive Medicine, Univ. Oregon, Health Sciences Center, Portland, OR 97201); Bingham, E. L. *J Natl Cancer Inst* 58(5): 1225-1228; 1977.

Serum properdin levels were measured in 21 benzidine operators at 6-mo intervals for 2 yr after termination of exposure to the carcinogen. Seven of the subjects had developed bladder cancers within a 4-mo period prior to the initial assay, and all seven had properdin levels below the median for the group. Two of the three workers with prior brief exposure to β -naphthylamine developed benign bladder tumors but no malignant tumors up to 13 yr later. Properdin levels in these three men were consistently at or above median values. Men exposed to benzidine for < 6 yr did not develop bladder tumors. Of four men whose properdin levels shifted from high to low, three developed bladder cancers 0.5, 4, and 9 yr later. Only one man whose properdin level remained high developed bladder cancer 7 yr later, and his immunologic status may have been complicated by an earlier laryngeal tumor. Bladder tumors recurred only in five men with consistently low properdin levels. (19 refs.)

77-6854 Formation of Methylhydrazine from Acetaldehyde N-methyl-N-formylhydrazone, a Component of *Gyromitra esculenta*. (Eng) Nagel, D. (Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, Omaha, NB 68105); Wallcave, L.; Toth, B.; Kupper, R. *Cancer Res* 37(9): 3458-3460; 1977.

Experiments were performed to determine whether toxin from *Gyromitra esculenta* could lead to formation of the carcinogen methylhydrazine (MH) in vitro under pH conditions mimicking the human stomach, and in vivo MH production in female Swiss mouse stomach. Under pH 1 to 3 conditions gyromitrin (N-methyl-N-formylhydrazone) was converted to N-methyl-N-formylhydrazine (MFH), which was hydrolyzed to MH. The administration of 4.0 mg gyromitrin po to the mice produced MH values 6- to 30-fold higher than in controls. There was no correlation between time and the amount of MH present. These findings indicate that *G. esculenta* could present a carcinogenic as well as an acutely toxic health hazard. (22 refs.)

77-6855 Genetics of Colon Carcinogenesis in Mice Treated with 1,2-Dimethylhydrazine. (Eng) Evans, J. T. (Roswell Park Memorial Inst., Buffalo, NY 14263); Shows, T. B.; Sproul, E. E.; Paolini, N. S.; Mittleman, A.; Hauschka, T. S. *Cancer Res* 37(1): 134-136; 1977.

Colon papillomas and adenocarcinomas developed within 22 wk in 100% of ICR/Ha mice given weekly sc injections of 15 mg/kg 1,2-dimethylhydrazine (DMH). No tumors developed in identically treated C57BL/Ha mice during a 44-wk observation period. Genetic analysis of DMH colon carcinogenesis in the hybrid mice of these two strains showed that

susceptibility was dominant. Colon tumor incidence was 100% in reciprocal ICR/Ha x C57BL/Ha F₁ hybrids and in the susceptible backcross ICR/Ha x F₁. Tumor yield was 78% in F₂ hybrids and 38% in resistant backcross mice of genotype C57BL/Ha x F₁. Tests with five isozyme markers and two coat color genes appeared to rule out linkage of DMH susceptibility on seven autosomes. A 47% tumor incidence among male resistant backcross hybrids, regardless of whether their single X chromosome was inherited from the ICR/Ha or C57BL/Ha strain, was evidence against sex linkage. (11 refs.)

- 77-6856 **Morphological Studies of Chemically Induced Colon Tumors in Hamsters.** (Eng.) Winneker, R. C. (Dept. Physiology and Biophysics, Univ. Illinois, Urbana, IL 61801); Tompkins, M.; Westenberger, P.; Harris, J. *Exp Mol Pathol* 27(1): 19-34; 1977.

Light and electron microscopy was used to examine progressive histopathological changes over a 21-wk period in the colons and livers of male LHC/Lak cream hamsters receiving 1,2-dimethylhydrazine (DMH: 20 mg/kg/wk x 17, sc). The animals were sacrificed on a weekly basis. After 15 injections, all 17 remaining animals had neoplastic lesions of the colon. Adenocarcinoma in situ was found in 10, invasive adenocarcinoma in 7, of which 5 also had liver metastases. Tumor progression followed a course of colonic enteritis (5 wk), focal atypias (7 wk), glandular dysplasias (10-14 wk), carcinoma in situ (15 wk), and invasive adenocarcinoma (17 wk). The toxic effect of DMH on the liver was pronounced and was associated with some of these progressive morphological changes. (34 refs.)

- 77-6857 **Surface Changes in the Descending Colon of Rats Treated with Dimethylhydrazine.** (Eng) Barkla, D. H. (Dept. Anatomy, Monash Univ., Clayton, Victoria, Australia, 3168); Tutton, P. J. *Cancer Res* 37(1): 262-271; 1977.

Male Sprague-Dawley rats were inoculated sc with 21 mg/kg/wk of 1,2-dimethylhydrazine for up to 20 wk, and morphological changes that occurred on the luminal surface of the descending colon were noted. The animals were killed at 2-wk intervals over a period of 30 wk. Scanning electron microscopy revealed changes as early as 4 wk: there was a progressive replacement of the normal epithelial cells with enlarged and irregularly shaped arrangements of epithelial cells; the entire surface was disorganized by 30 wk. Tumors were apparent by 18 wk, and by 30 wk all animals had tumors. The tumor cells were smaller, more rounded, showed less regularly shaped microvilli, and had fewer particles in the apical surface membrane than normal absorptive cells. The malignant sites were not related to specific sites of morphologic change but occurred in generally disordered mucosa. (11 refs.)

- 77-6858 **Partial Inhibition of Postreplication Repair and Enhanced Frequency of Chemical Transformation in Rat Cells Infected with Leukemia Virus.** (Eng) Waters, R. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830); Mishra, N.; Bouck, N.; DiMayorca, G.; Regan, J. D. *Proc Natl Acad Sci USA* 74(1): 238-242; 1977.

Postreplication DNA repair and chemical transformation with 4-nitroquinoline 1-oxide (4-NQO) were studied in rat cell lines uninfected or infected with Rauscher leukemia virus (RLV) to clarify the leukemia virus-induced sensitization of rat cells. Equivalent amounts of carcinogen were bound to the DNA initially and removed during excision repair. The lines differed, however, in that the infected line exhibited both sensitivity to 4-NQO-induced transformation and a partial inhibition of postreplication repair after 4-NQO or UV-treatment. It has not been determined whether the response is a general effect of leukemia virus infection or it is limited to RLV interaction with rat cells. If it is a general result of leukemia virus infection, the role of leukemia viruses in the etiology of leukemia is to sensitize the infected cell to spontaneous transforming mutations. (24 refs.)

- 77-6859 **Proteolysis Associated with Normal, Carcinogen-treated, and Transformed Rat Liver Epithelial Cells.** (Eng) Tokes, Z. A. (Cell Membrane Section, Los Angeles County/Univ. Southern California Cancer Center, Los Angeles, CA 90033); Sorgente, N.; Okigaki, T. *Prog Clin Biol Res* 17: 615-624; 1977.

A method using ¹²⁵I-labeled protein substrate covalently linked to modified latex beads was developed to distinguish between cell-surface-associated and released proteolytic activity. These beads are rolled over the surface of the cultured cells or next to the cells. This method was applied to normal, carcinogen-treated, and spontaneously transformed rat liver epithelial cells. Transformed cells always released greater amounts of radioactivity than carcinogen-treated or normal hepatocytes when the beads were presented next to the cells, indicating an enhanced release of proteolytic enzymes. When the substrate was in contact with the viable cell surfaces, both the carcinogen-treated and transformed cells released more radioactivity from the beads' surface than the normal cells. This enhanced proteolytic cleavage indicates that there is an altered surface topology in an increased surface-associated enzyme activity on both the carcinogen-treated and transformed cells. (16 refs.)

- 77-6860 **Similarity of the Mechanism of Chemical Carcinogen-initiated Teratogenesis and Carcinogenesis in Mice.** (Eng) Nomura, T. (Dept. Genetics, Univ. Wisconsin, Madison, WI 53706). *Cancer Res* 37(4): 969-973; 1977.

Transmaternal exposure of ICR/Jcl mice embryos to the max tolerated dose (15 µg/g sc) of the carcinogen 4-nitroquinoline

1-oxide (4-NQO) induced neither fetal deaths nor malformations, although these embryotoxicities were detected with urethan (1,000 $\mu\text{g/g}$ sc) and x-rays (216 rads). Direct injection of 4-NQO into the amniotic cavity induced a high incidence of malformations, indicating that the previous lack of teratogenicity was due to failure of the compound to reach the embryo. Similarities in the mechanism of chemical-induced teratogenesis and carcinogenesis were also suggested by the ability of caffeine to inhibit urethan-initiated teratogenesis when administered up to 48 hr after urethan, but not when administered during the 48- to 72-hr posturethan or the 6- to 30-hr preurethan periods. These results are similar to those observed in 4-NQO-initiated transformation in cultured mouse embryo cells and in 4-NQO- and urethan-initiated lung tumorigenesis in the mouse fetus. Thus, the mechanism of 4-NQO and urethan teratogenesis and carcinogenesis may be related to error-prone postreplication DNA repair. (38 refs.)

- 77-6861 **Carcinogenesis in Tissue Culture. 28. Comparison of Various Effects of a Chemical Carcinogen, 4-Nitroquinoline 1-Oxide, on Normal Human Cells and on Normal Mouse Cells in Culture.** (Eng) Namba, M. (Dept. Pathology, Kawasaki Medical Sch., 577 Matsushima, Kurashiki 701-01, Japan); Nishitani, K.; Kimoto, T. *Jpn J Exp Med* 47(4): 263-269; 1977.

The effects of 4-nitroquinoline 1-oxide (4NQO) on normal human embryo cells resistant to in vitro transformation with 4NQO were compared with its effects on easily transformable normal C3H/HeN mouse embryo cells. The following effects of 4NQO on normal human and murine cells were examined: (1) cytotoxicity; (2) DNA, RNA, and protein synthesis; (3) incorporation of 4NQO into cells and time course changes of the drug bound with macromolecular substances in the cells; (4) DNA repair synthesis; and (5) chromosomal changes. The results demonstrated that there were no differences in cytotoxicity and inhibition of cellular macromolecular synthesis between human and mouse cells. On the other hand, significant differences were noted in DNA repair synthesis and chromosome aberrations between the two types of cells. DNA repair synthesis of human cells was very efficient compared to that of mouse cells. Chromosome abnormalities of human cells were 13%, while those of mouse cells reached a percentage of 32% to 36%. These differences may be related to the increased sensitivity of mouse cells to chemical carcinogens. (16 refs.)

- 77-6862 **Organ-specific Effects of the Carcinogen Methylazoxymethanol Related to Metabolism by Nicotinamide Adenine Dinucleotide-dependent Dehydrogenases.** (Eng) Grab, D. J. (Dept. Cell Biology, Rockefeller Univ., 1230 York Ave., New York, NY 10021); Zedeck, M. S. *Cancer Res* 37(11): 4182-4189; 1977.

Methylazoxymethanol acetate (MAM acetate) selectively induces a high incidence of tumors in rat liver and colon after a single treatment. The mechanism for this organotropism is unclear, but it has been suggested that MAM might be converted by alcohol dehydrogenase to a reactive aldehyde form. Enzyme activity dependent on nicotinamide adenine dinucleotide (NAD⁺) and NADP was determined in 169,000 \times g supernatants from tissues sensitive and resistant to MAM. Liver fractions were most active in changing NAD⁺ to its reduced form with MAM as a substrate; the colon and cecum were also active. The jejunum and ileum, resistant to the acute and chronic effects of MAM, showed little NAD⁺-dependent dehydrogenase activity when either ethanol or MAM was used. In some tissues, NADP was changed to its reduced form in the presence of MAM. The 35% to 75% ammonium sulfate pellet of the liver 169,000 \times g supernatant was fractionated by gel filtration. MAM NAD⁺-dependent activity coincided with alcohol dehydrogenase activity, suggesting that MAM is acted on by an alcohol dehydrogenase-like enzyme. Pyrazole, an inhibitor of alcohol dehydrogenase, blocked NAD⁺ reduction in the presence of MAM. In addition, MAM was a substrate for purified horse liver alcohol dehydrogenase. Pyrazole given to rats 2 hr prior to the carcinogen prevented MAM-induced lethality. The data suggest that NAD⁺-dependent enzymatic reactions in tissue cytosol may be responsible for the organ-specific effects of MAM in the rat. (23 refs.)

- 77-6863 **Differences in the Acute Response of the Various Segments of Rat Intestine to Treatment with the Intestinal Carcinogen, Methylazoxymethanol Acetate.** (Eng) Zedeck, M. S. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Grab, D. J.; Sternberg, S. S. *Cancer Res* 37(1): 32-36; 1977.

The acute pathological and biochemical alterations induced by methylazoxymethanol acetate (MAM acetate, 35 mg/kg, iv) in the different segments of the Sprague-Dawley rat small intestine and colon are described. Karyorrhexis was found in the duodenum, cecum, and all segments of the colon at 6 hr after treatment. Much of the cellular debris was removed by 24 hr, although mitoses did not return to normal levels until the third day. No pathological alterations were found in the jejunum or ileum, even as late as 24 hr after treatment. Studies of DNA synthesis at 24 hr indicated that the jejunum and ileum were much less affected than the duodenum, cecum, or colon. In contrast, 5-fluorouracil (25 and 50 mg/kg, iv) and nitrogen mustard (2 mg/kg, iv), agents that inhibit proliferating cells but are not known to be intestinal carcinogens, affected all of the segments equally. The results indicate that a correlation exists between those segments of intestine acutely affected by MAM acetate and the sites of eventual tumor development. The level of deacetylase activity in the various segments did not correlate with sensitivity to MAM acetate-induced inhibition of DNA synthesis. The agent also inhibited duodenal and colonic DNA synthesis in rats with

cannulated bile ducts. This indicates that the carcinogen does not require biliary transport to the intestinal lumen to exert its biological effects. Mechanisms that might account for the selectivity of MAM acetate activity in the various intestinal segments are discussed. (17 refs.)

77-6864 **Enhancement of Chemically-induced Neoplasia by Proximal Enterectomy** (Meeting Abstract). (Eng.) Williamson, R. C. (United Bristol Hosp., Bristol, England); Bauer, F. L.; Malt, R. A. *Br J Cancer* 36(3): 401; 1977. (1 ref.)

77-6865 **Effect of Prolactin on Growth and the Estrogen Receptor Level of Human Breast Cancer Cells (MCF-7)**. (Eng) Shafie, S. (Dept. Biochemistry, Wayne State Univ. Sch. Medicine, Detroit MI 48201); Brooks, S. C. *Cancer Res* 37(3): 792-799; 1977.

The effect of prolactin on the estrogen receptor (E_2R) level and growth of human MCF-7 breast cancer cells was investigated. Concentrations of either 0.19 or 7.38 nanomolar 17β -estradiol (E_2) reached an equilibrium in the binding reaction after 30 min of incubation. Both ovine (10 μ g/ml) and human (5 μ g/ml) prolactin doubled the E_2R level, with the latter being at least 10 times more stimulatory on a concentration basis. Approx 80% of the E_2R was transported to the nucleus, and the prolactin stimulation was reflected in an elevated nuclear uptake of tritiated E_2 . The growth rate was not altered with either prolactin. Insulin (10 μ g/ml) had no effect on E_2R concentration. N^6, O^2 -Dibutyryl cyclic AMP (10^{-4} M) increased the insulin stimulation of tritiated thymidine incorporation and brought about a prolactin stimulation of apparent DNA synthesis. Theophylline (10^{-3} M) blocked both these events. The possible mechanism implicating prolactin as an effector of the differentiation and growth of MCF-7 cells is discussed. (53 refs.)

77-6866 **Liver Lesions and Oral Contraceptive Steroids**. (Eng) Barrows, G. H. (Dept. Pathology, Health Sciences Center, Univ. Louisville, Louisville, KY 40201); Christopherson, W. M.; Drill, V. A. *J Toxicol Environ Health* 3(1/2): 219-230; 1977.

CF-LP and random-bred Swiss-Webster mice were evaluated for liver neoplasms after the administration of oral contraceptive steroids (mestranol, norethynodrel, or norethynodrel-mestranol). There was no increased incidence of hepatocellular tumors beyond the variation expected by chance. The overall tumor incidence in treated and untreated groups was identical. Tumor size did not increase significantly in the treated animals. Liver wt progressively increased in several treated groups. In both treated and

untreated animals, hepatocellular lesions were usually accompanied by intracytoplasmic inclusions similar to those observed in human liver tumors. Vascular lesions occurred in some animals receiving large doses of contraceptive steroids. They may be the result of local toxicity, but their similarity to lesions in benign liver tumors warrants further investigation. No evidence was found that contraceptive steroids act as initiators of liver neoplasia. (13 refs.)

77-6867 **Mammary Tumorigenesis and Pathologic Changes in Female Mice Fed Diets Containing Diethylstilbestrol or Estradiol- 17β** (Meeting Abstract). (Eng.) Norvell, M. J. (Hormone Res. Program, Natl. Center for Toxicological Res., Jefferson, AR); Highman, B.; Farmer, J. H.; Shellenberger, T. E. *J Toxicol Environ Health* 3(1/2): 367-368; 1977. (no refs.)

77-6868 **Results of an 8-Yr Study on the Toxicological Evaluation of Animal Feed Additives by the Relay Toxicity Method**. (Fre.) Truhaut, R. (Laboratoire de Toxicologie et d'Hygiene industrielle, Faculte des Sciences pharmaceutiques et biologiques de Paris-Luxembourg, 4, avenue de l'Observatoire, 75006, Paris, France); Ferrando, R. *Eur J Toxicol* 9(7): 413-422; 1976.

The principles of a new method for the toxicological evaluation of animal feed additives such as diethylstilbestrol (DES), estradiol-progesterone (EP), estradiol-testosterone (ET) and Carbadox (CX) are presented. This method, the relay toxicity assay, can determine the potential toxicity of meat from animals that were given chemicals for growth. CX (200 ppm) was fed to pigs for > 1 mo. After being fed a diet of pork from these pigs for 2 and 7 yr, respectively, rats and beagle dogs showed no growth or reproduction abnormalities. No harmful effects to humans were demonstrated by extrapolating the coefficient of consumption from animals to humans. Rats that were fed calf meat for 20-24 mo from calves that had received two implants of DES (24 mg/calf) had low body wt and were sterile. Furthermore, despite the absence of genital tract lesions, the number of second litters of rats given a 6% diet of liver from DES-treated calves was lower than calves was lower than that for other animals. There was no potential danger with ET or EP, but DES presents marked danger to the consumer. (11 refs.)

77-6869 **Induction of Urogenital Anomalies and Some Tumors in the Progeny of Mice Receiving Diethylstilbestrol During Pregnancy**. (Eng) Nomura, T. (First Dept. Surgery, Osaka Univ. Medical Sch., Fukushima-ku, Osaka 553, Japan); Kanzaki, T. *Cancer Res* 37(4): 1099-1104; 1977.

Pregnant ICR/Jcl mice were given a single dose (10 µg/g, sc) of diethylstilbestrol (DES) on gestation days 7-10. Treatment with DES on days 15-19 resulted in the induction of persistent urogenital sinus in 15.8%-92.5% of the female offspring and hypertrophy of the portio vaginalis in 11.8%-73.3%. Treatment on days 17 and 19 resulted in undescended testes and their hypogenesis in 70.4%-73.3% of the male offspring. Treatment with DES at other stages of pregnancy and after birth did not cause these alterations. The incidence of ovarian and lung tumors increased significantly (31.0%-37.9%) when DES was given on days 15 and 17. However, adenosis and adenocarcinoma of the vagina were not observed in the offspring. (39 refs.)

77-6870 Upper Genital Tract Changes Associated with Exposure In Utero to Diethylstilbestrol. (Eng)

Kaufman, R. H. (Dept. Obstetrics and Gynecology, Baylor Coll. Medicine, 1200 Moursund Ave., Houston, TX 77030); Binder, G. L.; Gray, P. M.; Adam, E. *Am J Obstet Gynecol* 128(1): 51-59; 1977.

Hysterosalpingograms of 46 young women with documented in utero exposure to diethylstilbestrol (DES) and 14 with suspected exposure were compared with those of 23 women being investigated for infertility. The DES doses received by the mothers in the documented cases ranged from 5-300 mg/day; the mean age of this group was 22.3 yr. Significant changes were detected in the uterus of 40 of the DES-exposed women. These changes consisted of a T-shaped appearance of the uterus in 21 cases, constricting bands in the uterine cavity, a hypoplastic uterus, and, less frequently, intrauterine polypoid defects, synechiae, and a unicornuate uterus. The largest proportion of uterine changes occurred in women exposed to DES prior to the 18th wk of gestation. In 36/40 women, gross defects were also noted in the cervix; these included an anterior cervical ridge, a cervical hood, a hypoplastic cervix, and a pseudopolyp appearance. None of the 23 controls exhibited comparable uterine or cervical defects. (12 refs.)

77-6871 Strain Differences in the Response of the Mouse to Diethylstilbestrol. (Eng) Greenman, D. L.

(Div. Molecular Biology, Natl. Center Toxicological Res., Jefferson, AR 72079); Dooley, K.; Breeden, C. R.; Gaas, G. H. *J Toxicol Environ Health* 3(3): 589-597; 1977.

About 400 mice of each genetic population (BALB/c StCr1fC3Hf/Nctr, C57BL/6J, (C57BL/6 x BALB/c)_{F1} hybrid (B6CF₁), and monohybrid-cross offspring of B6CF₁ mice) were used to examine their uterine, vaginal, and thymus responses to diethylstilbestrol (DES). Weanling mice were fed DES at concentrations of 2.5-1,000 ppb (µg/kg feed) for 6 days and then killed about 20 hr after removal of the feed. C57BL/6, B6CF₁, and the monohybrid-cross offspring did not differ in the uterine-wt response to DES, but the slope of the dose-response line was shallower for the BALB/c than for the other strains.

Dietary DES concentrations ≥ 250 ppb inhibited the uterotrophic response in all populations. Vaginal cornification occurred at lower concentrations of DES in the C57BL/6 strain than in the B6CF₁ animals. BALB/c and monohybrid-cross offspring were indistinguishable from each other in their vaginal response to DES, and they were less sensitive to DES than the other populations. The use of ethanol or corn oil as the solvent for DES had no apparent effect on uterine wt or vaginal response in any of the mice. DES depressed thymus wt in a dose-related fashion at dietary concentrations ≥ 100 ppb in all genetic populations. These results provide the information needed to interpret carcinogenic dose-response curves for the same mouse strains and crosses. (18 refs.)

77-6872 The Pars Intermedia and Renal Carcinogenesis in Hamsters. (Eng) Hamilton, J. M. (Dept. Experimental Pathology and Cancer Res., Sch. Medicine, Univ. Leeds, Leeds, England); Saluja, P. G.; Thody, A. J.; Flaks, A.

Eur J Cancer 13(1): 29-32; 1977.

The production of melanocyte-stimulating hormone (MSH) by the intermediate lobe of the pituitary was investigated in male Syrian golden hamsters receiving one sc injection of 0.6 mg diethylstilbestrol (DES) three times per week to a total dose of 65 mg over 9 mo. All treated animals that survived the experiment developed kidney tumors that were bilateral and cortical in distribution. The pituitary glands of the treated animals were larger and significantly heavier than those of controls. The enlargement was mainly restricted to the intermediate lobe. The main alteration was a significant increase in the number of prolactin-secreting cells and a decrease in the number of somatotrophin-secreting cells and basophils. The cells were hypertrophic and hyperplastic, with evidence of mitosis. Infiltration of the posterior lobe and infundibular stalk by cells of the intermedia was common. Total pituitary immunoreactive α-MSH in controls was 471 nanograms (ng)/gland, corresponding to a concentration of 146 ng/mg wet wt. The corresponding figures for the DES-treated animals were 14,810 ng/gland and 360 ng/mg wet wt; the differences were statistically significant. The serum concentration of MSH averaged 452 picograms (pg)/ml, compared to 3,190 pg/ml in the treated animals. Serum levels of MSH were consistently higher in the treated animals. It is possible that kidney tumor induction by estrogens in male hamsters is mediated by the pituitary gland and that MSH plays a role in this process. (12 refs.)

77-6873 The Impact of Long Term Estrogen Support After Hysterectomy: A Report of 1016 Cases. (Eng.) Byrd, B. F. (Dept. Surgery, Vanderbilt Univ. Sch. Medicine, Nashville, TN); Burch, J. C.; Vaughn, W. K. *Ann Surg* 185(5): 574-580; 1977.

Follow-up studies are reported for a series of 1,016 women who were placed on estrogen support following hysterecto-

Every woman was operated on at least 5 yr ago, with the series dating back 28 yr for the earliest participants. The women ranged from 22 to 78 yr in age. Support was principally conjugated estrogen at the usual dose 1.25 mg/day. There was a marked drop in the deaths from breast cancer cases (54) over those that were expected (149). This was principally due to the diminished number of deaths from heart attack and cancer. There was also marked improvement in the clinical evidence of osteoporosis. There was a slight drop in mortality from breast cancer in this group but an increase in the total number of breast cancers. The risk factors known to exist for breast cancer (age, late menopause, and nulliparity) are effective in women who are placed on estrogen support, justifying special consideration in evaluating the need of this group of individuals. However, general impact of long-term estrogen support following hysterectomy is favorable. (8 refs.)

77-6874 **Estrogen and Endometrial Carcinoma. An Independent Pathology Review Supporting Original Risk Estimate.** (Eng) Gordon, J. (Dept. Res. and Education, Kaiser-Permanente Medical Center, 4900 Sunset Blvd., Los Angeles, CA 90027); Reagan, J. W.; Finkle, W. D.; Ziel, H. K. *N Engl J Med* 297(11): 570-571; 1977.

Three expert pathologists independently reviewed slides of specimens obtained by endometrial biopsy and curettage. These slides had formed the basis for an initial report that stated that estrogen therapy increases the risk of endometrial carcinoma. However, it is possible that the hazard of estrogen therapy may have been exaggerated by the inclusion of patients with atypical endometrial hyperplasia among those with endometrial carcinoma. All three pathologists agreed that 66/89 of the original slides had been interpreted correctly. Of these 66 patients with a unanimous diagnosis, 50 had used conjugated estrogens, compared to 54/94 in the original study. A recalculation of the original risk ratio estimate of 7.6, in which the data were restricted to the 66 patients and 132 matched controls in whom diagnosis was unanimous, gave a new estimate of 8.1. This independent review of the original material, therefore, supports the conclusion that conjugated estrogens play a part in the pathogenesis of endometrial cancer. (8 refs.)

77-6875 **Long-Term Effects of Neonatal Treatment with Progesterone, Alone and in Combination with Estrogen, on the Mammary Gland and Reproductive Tract of Female BALB/cfC3H Mice.** (Eng) Jones, L. A. (Dept. Zoology, Univ. California, Berkeley, CA 94720); Bern, H. A. *Cancer Res* 37(1): 67-75; 1977.

The vaginal and mammary responses of BALB/cfC3H/Crgl mice to neonatal progesterone (P) treatment were investigated. The mice received daily sc injections of 5 or 20 μ g 17 β -estradiol (E) or 100 μ g P; 5 μ g E + 100 μ g P; or 20 μ g E + 100 μ g P for 5 days beginning within 36 hr of birth. Half the animals in each group were ovariectomized on day 40, and all were killed at the onset of tumor growth or at 12 mo of age. Mice receiving 100 μ g P alone showed ovary-dependent persistent vaginal cornification. When P + E were administered concurrently, the occurrence of persistent vaginal cornification was significantly lower than that with E alone. P + E also resulted in a lower incidence of lesions, but they were of greater severity. P alone produced hyperplastic downgrowths and lesions of the vaginal and cervical epithelia, but to a lesser degree than those in mice receiving E. The low doses of P and E used lesser each resulted in an earlier age of onset and a higher incidence of mammary tumors; this was also noted after both combined treatments. Ovariectomized mice did not develop mammary tumors, regardless of neonatal treatment. Thus, neonatal P affects both the genital tract and mammary glands of female mice. These results indicate that progestins and estrogens should be administered cautiously to pregnant women. (38 refs.)

77-6876 **Sex Steroids as a Cause of Adenocarcinoma of the Dorsal Prostate in Nb Rats, and Their Influence on the Growth of Transplants.** (Eng.) Noble, R. L. (Univ. British Columbia, Cancer Res. Center, Vancouver, British Columbia, Canada). *Oncology* 34(3): 138-141; 1977.

The incidence of grossly recognizable adenocarcinoma of the prostate increased from approx 0.5% to 20% of Nb rats following prolonged treatment with pellets of testosterone propionate (TP), alone or with estrone, inserted sc. The effect of these sex steroids on the growth of tumor transplants inserted into the back of the neck of rats was studied. Most transplants were autonomous and not influenced by hormones. However, an exceptional prostatic tumor, which showed hormone dependence, arose in a rat after removal of an EP pellet (10-mg pellet containing 90% estrone, 10% cholesterol), but with no subsequent treatment. This tumor would only grow in estrogenized hosts. Removal of estrogen from animals with growing tumors led to tumor regression, but removal of estrogen from animals with autonomous tumors led to eventual regrowth of these transplanted tumors. Replacement with lower doses of estrogen reduced the extent of regression and prevented autonomous change. When a regressed estrogen-dependent tumor was exposed to prolonged treatment with TP, eventual regrowth was androgen-dependent, and the tumor would not grow in estrogenized rats. Apparently, progression from estrogen to androgen dependency could be directed by this procedure. (8 refs.)

77-6877 **C₁₉-Steroid Metabolism by Spontaneous Adenocarcinoma of the A x C Rat Ventral Prostate.** (Eng) Shain, S. A. (Southwest Foundation Res. and Education, Post Office Box 28147, San Antonio, TX 78284); Nitchuk, W. M.; McCullough, B. *J Natl Cancer Inst* 58(3): 747-752; 1977.

Ventral prostate specimens from 37- to 46-mo-old A x C rats treated with a single im injection of 15 mg testosterone-p-hexoxyphenyl propionate (Andradurin) demonstrated three primary morphologic patterns, each of which was divisible into two subgroups based on the extent of glandular alteration. The principal groups were: hyperplasia (1), atypical hyperplasia (2), and adenocarcinoma (3). The secondary classifications were subgroup (+), few glands involved, and subgroup (++) , most glands involved. Multiple parameters of the ventral prostate testosterone metabolic potential failed to distinguish the morphologically diverse prostate specimens of groups 1(+), 1(++), 2(+), 2(++), and 3(+), which predominantly metabolized testosterone to 5 α -reduced 17 β -hydroxysteroids. By contrast, testosterone metabolism by ventral prostate specimens of group 3(++) was distinct from all other prostate specimens. The distin-

guishing feature was a shift to more prominent elaboration of 17-ketosteroids, principally δ^4 -androstenedione and a concomitant decreased production of 5 α -reduced 17 β -hydroxysteroids. The change in this biochemical parameter of prostate epithelial cell function was an early manifestation of the neoplastic process. (22 refs.)

See also:

- *(Rev.): 77-6601, 77-6602, 77-6603, 77-6604, 77-6605
77-6606, 77-6607, 77-6608, 77-6609, 77-6610
77-6611, 77-6612, 77-6613, 77-6614, 77-6615
77-6616, 77-6617, 77-6618, 77-6619, 77-6620
77-6621, 77-6622, 77-6623, 77-6624, 77-6625
77-6626, 77-6628, 77-6629, 77-6655, 77-6656
77-6657, 77-6658, 77-6664, 77-6666.
- *(Phys.): 77-6879, 77-6896, 77-6897, 77-6906, 77-6914.
- *(Viral): 77-6955, 77-6956, 77-6970, 77-7004.
- *(Immun.): 77-7033, 77-7044, 77-7048, 77-7061, 77-7069
77-7083, 77-7086, 77-7087.
- *(Path.): 77-7108, 77-7109, 77-7115, 77-7116, 77-7137
77-7142, 77-7144.
- *(Epid.-Biom.): 77-7157, 77-7159, 77-7164, 77-7171, 77-7172
77-7173, 77-7174.

PHYSICAL CARCINOGENESIS

- 77-6878 **The Role of the Mineral and Organic Components of Bony Tissue in ^{239}Pu Metabolism.** (Rus) Shvydko, N. S. (Scientific Res. Inst. Radiation Hygiene, Russian SFSR Ministry Public Health, Leningrad, USSR); Rushonik, S. I.; Vorozhtsova, L. N.; Popov, D. K. *Med Radiok (Mosk)* 22(9): 52-55; 1977.

The roles played by the inorganic and organic components of bony tissue in ^{239}Pu turnover were studied in rats 1 hr to 4 mo after iv administration of the isotope (4 $\mu\text{Ci}/\text{animal}$). The mineral fraction contained 19% of the isotope 1 hr after administration, and 26% at 20 days to 4 mo. The isotope content in the organic fraction decreased accordingly from 81% at 1 hr to 74% after 4 mo. Within the organic fraction, the av isotope content was 20% in the albumin fraction (13% after 1 hr, 23% after 4 mo), 6% in the mucin fraction (12% after 1 hr, 1% after 4 mo), 3% in the residual proteins (8% after 1 hr, 3% after 4 mo), and 71% in the collagen (67% after 1 hr, 73% after 4 mo). Forty-five per cent of the collagen-bound isotope was easily desorbed by sodium citrate, but the rest was bound firmly, which indicates the involvement of chemical reaction and electrostatic adsorption in the sorption of ^{239}Pu by collagen. (9 refs.)

- 77-6879 **Effect of Inhaled Plutonium Dioxide on Development of Urethane-induced Pulmonary Adenomas.** (Eng) Brightwell, J. (Dept. Pathology, Univ. Newcastle upon Tyne, Newcastle upon Tyne, England); Heppleston, A. G. *Br J Cancer* 35(4): 433-438; 1977.

Male A2G mice were exposed to 25 nanocuries of $^{239}\text{PuO}_2$ aerosols 2 wk before or after injection of 1 mg/kg urethane ip to determine the effect of Pu on urethane carcinogenesis. Two types of experiments were conducted: (1) Pu inhalation followed by urethane (PU), mock inhalation followed by urethane (MU), and inhalation or mock inhalation followed by saline (PS or MS); (2) urethane followed by Pu (UP), urethane followed by mock inhalation (UM), or saline followed by inhalation or mock inhalation, (SP or SM). In experiment 1, the incidence of pulmonary adenomas was higher in MU and PU animals than in saline-treated animals 8 wk after injection. However, 16 wk after injection, there were significantly more tumors in MU mice than in PU mice. Although the number of tumors in both groups increased with time, the increase was faster in the MU mice, and their tumors were larger. PU tumors had higher mitotic and labeling indexes than MU tumors. In experiment 2, there were more tumors in the urethane-treated animals than in those receiving saline, but the number of tumors and their rate of increase were greater in UM mice than in UP mice. UM mice had significantly

larger tumors 12, 24, and 36 wk after injection. The labeling index was much higher in UP mice than in UM mice at 24 and 36 wk. The number of tumors per animal was similar regardless of whether urethane was administered before or after Pu or whether the exposure was mock. The initial radiation dose to the lung was about 0.3 Gray unit (Gy)/day, which decreased to 0.014 Gy/day at 36 wk. The accumulated dose was 10 Gy. These results are discussed in terms of the degenerative epithelial changes that follow Pu exposure. It is concluded that damage at the cellular level may account for the reduced growth of pulmonary adenomas in mice whose lungs contained Pu particles. (14 refs.)

- 77-6880 **Inhalation Carcinogenesis of High-fired $^{238}\text{PuO}_2$ in Rats.** (Eng.) Sanders, C. L. (Biology Dept., Battelle, Pacific Northwest Labs., Richland, WA 99352); Dagle, G. E.; Cannon, W. C.; Powers, G. J.; Meier, D. M. *Radiat Res* 71(3): 528-546; 1977.

A group of 294 female Wistar rats were examined over their life span after receiving a single nose-only exposure to aerosols of $^{238}\text{PuO}_2$ for 30 min. The activity median aerodynamic diameter of the $^{238}\text{PuO}_2$ averaged 1.80 μm . Radiation pneumonitis was present in groups of animals receiving 220 and 890 nanocuries (nCi) ^{238}Pu , and it was the probable cause of death in most rats receiving the higher dose. No metaplastic lesions were found in any of the unexposed control rat lungs (50 rats). A total of 33 primary lung tumors were induced in the exposed animals: 18 adenocarcinomas, 13 squamous cell carcinomas, 1 fibrosarcoma, and 1 pleural mesothelioma. Squamous cell carcinomas were most common at the 220- and 890-nCi levels, but only adenocarcinomas were found at the 11-nCi level. Total lung tumor incidences were 0% for unexposed rats, 0.8% for an intraalveolar deposition of 0.14 nCi, 7.5% for 11 nCi, 60% for 220 nCi, and 19.2% for 890 nCi ^{238}Pu . Radiation dose analyses demonstrated a significant increased incidence of lung tumors, compared to controls, only at a dose of 1,720 rads. High-fired $^{238}\text{PuO}_2$ is less effective in inducing lung tumors in Wistar rats than $^{239}\text{Pu}_2$ (based on data from previous experiments); this may be a result of the smaller amount of lung tissue irradiated by the $^{238}\text{PuO}_2$ particles. (36 refs.)

- 77-6881 **Chromosome Aberrations Induced in Syrian Hamster Lung Cells by Inhaled $^{238}\text{PuO}_2\text{-ZrO}_2$**

Particles. (Eng) Stroud, A. N. (Mammalian Biology Group, Los Alamos Scientific Lab., Univ. California, Los Alamos, NM 87545). *Radiat Res* 69(3): 583-590; 1977.

Chromosomal analyses were performed on lung cells from Syrian hamsters that had been exposed to $^{238}\text{PuO}_2\text{-ZrO}_2$ microspheres in an inhalation chamber for 22 min. The lungs were removed 24 hr after exposure and placed in tissue culture for analysis. The incidence of chromosome aberrations 63 and 138 hr after cell cultivation increased (0.18 and 0.24 aberration/cell, respectively) above controls. The growth rate and mitotic indices were depressed greatly in cultures derived 1 and 3 wk after inhalation, compared to the values at 63 and 138 hr after culture. Autoradiographs revealed many alpha-track star clusters still in cultures derived 1 and 3 wk after inhalation, indicating that epithelial cells continued to be irradiated over those periods. The accumulated chromosome lesions, therefore, are a combination of the damage produced in vivo and in vitro. Examination of whole sections of hamster lungs exposed to plutonium microspheres by inhalation showed no histological effects. The data suggest that most cells with chromosome aberrations resulting in gene damage that disrupts normal growth are unable to survive and, therefore, are not potential cancer cells. Cells with minor aberrations that do not affect cell growth and function can survive with this lesion, so that, after several divisions, the damage may be expressed and the cells can then become genetically predisposed to malignancy. (15 refs.)

77-6882 Summary of Thyroid Findings in Marshallese 22 Years after Exposure to Radioactive Fallout. (Eng) Conard, R. A. (Medical Dept., Brookhaven Natl. Lab., Upton, NY 11973). In: *Radiation-associated Thyroid Carcinoma*. Degroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune Stratton): 539 pp.; 241-257; 1977.

The effects of exposure to ^{131}I , ^{132}I , ^{133}I , and ^{135}I were investigated in 62 inhabitants of Rongelap (R), 18 inhabitants of Ailingnae (A), and 151 inhabitants of Utirik (U) atolls in the Marshall Islands following exposure to radioactive fallout in 1954. The av dose to the thyroid, number of thyroid tumors, and number of thyroid cancers for the children (≤ 10 yr old) of R were 1,010 rads, 18/23, and 1/23; the corresponding figures for subjects > 10 yr were 379 rads, 6/45, and 3/45. For A, the figures for children were 382 rads, 2/6, and 0; those for subjects > 10 yr were 135 rads, 4/12, and 0. For U, the figures were 83 rads, 1/58, and 1/58 for children and 30 rads, 9/99, and 2/99 for older subjects. All seven thyroid cancer patients were women, and the latent period ranged from 11 to 22 yr. Four had metastases and five had multiple adenomas in the thyroid. It is estimated that the risk of cancer is 2.4 and 6.4 cases/ 10^6 rads/yr, for R children and older subjects, respectively, and 9.5 and 26.4 cases/ 10^6 rads/yr for U children and older subjects. Thyroids receiving lower doses developed tumors later than those receiving higher doses. Thyroxine treatment was initiated in 1965, but it is unknown

whether this prevented any development of nodules. It is suggested that the lower incidence in children in spite of higher doses was due to death of the injured cells at mitosis, leaving fewer cells to become malignant. (18 refs.)

77-6883 Action of Various ^{131}I Doses on the Natural and Radiation-induced Occurrence of Mammary Tumors in Rats. (Rus) Moskalev, Iu. I. (No affiliation given); Kalistratova, V. S. *Radiobiologiya* 17(3): 378-383; 1977.

The influence of the functional status of the thyroid gland, modified by the po administration of ^{131}I (0.001, 0.002, 0.01, 0.02, and 4 $\mu\text{Ci/g}$, corresponding to thyroid doses of 50, 100, 500, 1,000, and 200,000 rads), on the incidence of spontaneous and radiation-induced mammary gland tumors was studied in random-bred female albino rats aged 3-4 mo. Some groups received only ^{131}I , others received whole-body radiation (x-radiation: 100 rads, 10 rads/min, or gamma radiation: 300 rads, 16 rads/min), others received both. Small doses of ^{131}I (50-1,000 rads), which produced hyperthyroidism, increased the incidence of spontaneous breast tumors in nonirradiated rats and that of radiation-induced tumors in irradiated animals compared with controls. The increase was significantly higher in animals that received 500-1,000 rads of ^{131}I . The latency time was shorter than that in controls. These findings indicate the full summation of the effects of radiation, small doses of ^{131}I , and endogenous factors responsible for the induction of spontaneous tumors. The high dose of ^{131}I (4 $\mu\text{Ci/g}$), which resulted in hypothyroidism, significantly reduced the incidence of breast tumors compared with the spontaneous incidence. The experimental results indicate the major influence of the functional status of the thyroid gland on the incidence of spontaneous and radiation-induced breast tumors. (9 refs.)

77-6884 Role of the Thyroid and Parathyroid Glands in the Development of Osteosarcomas Induced by ^{90}Sr . (Rus) Semenova, V. P. (No affiliation given); Goloschapov, P. V.; Shvedov, V. L. *Med Radiol (Mosk)* 22(9): 40-44; 1977.

The influence of the thyroid and parathyroid glands on the bone tumor-inducing effect of ^{90}Sr (0.3 $\mu\text{Ci/g}$ ip) was studied in male albino rats aged 3.5-4 mo. Group 1 received ^{90}Sr only, Group 2 underwent thyroidectomy, Group 3 thyroidectomy and parathyroidectomy, Group 4 parathyroidectomy 10 days before the administration of ^{90}Sr , and Group 5 received 500 μCi ^{131}I + ^{90}Sr . The bone tumor induction rates were 69/98 in Group 1 (88.1% osteosarcomas, 11.9% chondrosarcomas), 60/98 in Group 2 (98.3% osteosarcomas, 1.7% chondrosarcomas), 35/100 in Group 3 (97% osteosarcomas, 3% fibrosarcomas), 22/97 in Group 4 (95.2% osteosarcomas, 4.8% fibrosarcomas), and 2/207 in Group 5 (all osteosarcomas). The minimum

latency times were 185 days in Group 1, 143 days in Group 2, 160 days in Group 3, 210 days in Group 4, and 230 days in Group 5. The findings indicate that thyroidectomy alone has practically no influence on the bone tumor-inducing effect of ^{90}Sr , but simultaneous administration of ^{131}I nearly completely suppresses this effect. Tumor induction was also significantly reduced by parathyroidectomy with or without thyroidectomy. The experiments demonstrate the essential role of the endocrine system in blastomagenesis. (4 refs.)

77-6885 The Natural History of Radiation-associated Thyroid Cancer. (Eng) Roudebush, C. P. (Thyroid Study Unit, Univ. Chicago, Chicago, IL); DeGroot, L. J. In: *Radiation-associated Thyroid Carcinoma*. DeGroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): 539 pp.; pp. 97-118; 1977.

The clinical courses of 107 patients with radiation-associated thyroid cancer diagnosed between 1950 and 1975 were compared with those of 72 thyroid cancer age-matched controls without a history of radiation therapy. The mean age of the radiated subjects at diagnosis was 28.4 yr, and 36.4% were men. Although the mean interval between radiation and diagnosis was 17.8 yr, 10% had been treated > 30 yr prior to tumor development. Eighty percent of these patients had papillary tumors; no medullary or anaplastic tumors were observed. Of those with a radiation history, 41% had multifocal thyroid tumors compared with 19% of the controls. Ten recurrences were observed in the radiated population, but only 1 recurred in the controls. The higher incidence of recurrence in the former group was related to six recurrences in pediatric patients. Only a single thyroid cancer-specific death occurred in each group. Three parathyroid adenomas developed in the radiated subjects, none in the controls. These appeared an av of 33 yr after radiation. It is hypothesized that parathyroid adenoma may be a long-term complication of radiation to the head and neck. (16 refs.)

77-6886 Chronic Myeloid Leukaemia Following Radioiodine Therapy for Carcinoma Thyroid. (Eng) Bundi, R. S. (Inst. Radiotherapeutics, Glasgow, Scotland) Scott, J. S.; Halnan, K. E. *Br J Radiol* 50(589): 61-64; 1977.

Chronic myeloid leukemia (CML) occurred in a man who had been treated with radioiodine and megavoltage x-ray therapy for a well-differentiated adenocarcinoma of the thyroid. In December 1959, at age 42, the patient noticed a lump in his neck, for which a right hemithyroidectomy was carried out in March 1960. In view of palpable residual disease and blood vessel and lymphatic invasion, radiation therapy was applied to the neck and mediastinum. The total dose was 3,500 rads in 16 fractions over 21 days from a 4-MeV linear accelerator. Additional radiation was given in January 1971 when x-rays showed metastasis in the left humerus. It consist-

ed of a single dose of 1,500 rads from a ^{60}Co source. On five occasions from 1961 to 1971, the patient also received therapeutic doses of ^{131}I ; the total dose was 850 mCi, giving a blood dose of 325 rads and a bone dose of 260 rads. In between the radioiodine treatments he was put on thyroxine preparations. In November 1972, blood examination revealed a marked elevation of WBC and platelet counts. The WBC alkaline phosphatase reaction was weakly positive and was considered compatible with the diagnosis of CML. Bone marrow examination showed max cellularity, with a prominence of myelocytes and later forms of the myeloid series in the smears. The man died in March 1974 with widespread disease. Although the leukemogenic hazard of ^{131}I cannot be ruled out for this patient, it is possible that the development of CML was coincidental rather than due to radioiodine therapy. (17 refs.)

77-6887 Late Thyroid Sequelae of Radiation Therapy to the Upper Body. (Eng) Hamburger, J. I. (Northland Thyroid Lab., 20905 Greenfield-Suite 300, Southfield, MI 48075); Stoffer, S. S. In: *Radiation-associated Thyroid Carcinoma*. DeGroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): 539 pp.; 17-31 pp.; 1977.

Of 818 patients referred to Northland Thyroid Laboratory for thyroid evaluation in 1975-1976 because of prior radiation therapy to the neck and head, 16 (4 men and 12 women aged 21-60 yr) had thyroid cancer. Fourteen of the tumors were papillary and 2 were follicular. The interval between irradiation and diagnosis ranged from 14 to 40 yr. In the 14-yr period before the publicity about the relationship between radiation and thyroid cancer, only 25 patients with radiation-induced cancers were seen at the same laboratory. Thus, many other thyroid cancers will probably be detected if continued publicity is given to the problem. (10 refs.)

77-6888 Thyroid Neoplasms Following Irradiation in Infancy. (Eng) Hempelmann, L. H. (Dept. Radiology, Univ. Rochester Sch. Medicine, Rochester, NY). In: *Radiation-associated Thyroid Carcinoma*. DeGroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): 539 pp.; pp. 221-229; 1977.

Survey data on thyroid neoplasms in 2,872 thymus-irradiated subjects and their 5,055 nonirradiated siblings were analyzed statistically. Thyroid cancer developed earlier in life than benign tumors and primarily in males; benign goiters developed after small doses and predominantly in females. Females had a greater risk of developing thyroid cancer than males: 2.3 times for all females and 5 times for young adults. Except in

young adult females, there was no definite age effect. The risk of cancer was proportional to the thyroid dose, with a linear dose coefficient of $3.0/10^6$ persons/yr/rad for the total population and 4.8 for a high-risk group treated with large x-ray doses administered through wide ports. All Jews had a 3.4-fold greater risk than non-Jews, and young adult Jewish women had a 17-fold increased relative risk. (1 ref.)

77-6889 Histologic Parenchymal Changes in the Human Thyroid after Low Dose Childhood Irradiation.

(Eng) Straus, F. H. (Dept. Pathology, Univ. Chicago Sch. Medicine, Chicago, IL); Spitalnik, P. F. In: *Radiation-associated Thyroid Carcinoma*. DeGroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): 539 pp.; pp. 183-198; 1977.

Histologic changes were studied in thyroid tissues from 68 patients (aged 13-57 yr) with a history of childhood irradiation of the thyroid and with a palpable thyroid abnormality. Seven distinct categories of histologic changes were observed: focal hyperplasia (88% incidence), chronic lymphocytic thyroiditis (67%), single or multiple adenomas (51%), colloid nodules (51%), Hurthle cell changes (42%), fibrosis (25%), and well-differentiated carcinomas (59%). Of the carcinomas, 22% were papillary, 18% were follicular, and 60% were mixed papillary-follicular. These histologic changes appeared to result from the direct cell damage induced by ionizing radiation and the secondary effects of the thyroid stimulation that followed. (4 refs.)

77-6890 Thyroid Carcinoma after Head and Neck Irradiation: Evaluation of 1,476 Patients. (Eng)

Frohman, L. A. (Div. Endocrinology and Metabolism, Dept. Medicine, Michael Reese Medical Center, Chicago, IL 60616); Schneider, A. B.; Favus, M. J.; Stachura, M. E.; Arnold, J.; Arnold, M. In: *Radiation-associated Thyroid Carcinoma*. DeGroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): 539 pp.; pp. 5-15; 1977.

Physical and/or scintigraphic examination revealed evidence of nodular thyroid disease in 423/1,476 subjects who had received x-radiation to the head and neck for infectious and inflammatory disease. Of the 254 patients who underwent surgery, 92 had thyroid carcinomas and 160 had benign disease. The carcinomas were papillary (28), follicular (7), or a mixture of both elements (57). Multiple adenomas accounted for two-thirds of the benign disorders, and single adenomas, colloid cysts, Hurthle cell tumors, and thyroiditis accounted for the remainder. Benign tumors (most frequently adenomatous hyperplasia) coexisted with the carcinomas in 76% of the subjects. The absence of positive findings on palpation was not a reliable indicator of the absence of malignant disease, and the presence of multinodularity was not an indi-

cation of benign thyroid disease. The incidence of carcinoma in multinodular glands did not differ significantly from that in uninodular glands. (15 refs.)

77-6891 Risk Factors Associated with the Development of Thyroid Carcinoma and of Nodular Thyroid Disease Following Head and Neck Irradiation. (Eng)

Frohman, L. A. (Div. Endocrinology and Metabolism, Dept. Medicine, Michael Reese Medical Center, Chicago, IL 60616); Schneider, A. B.; Favus, M. J.; Stachura, M. E.; Arnold, J.; Arnold, M. In: *Radiation-associated Thyroid Carcinoma*. DeGroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): 539 pp.; 231-240 pp.; 1977.

Of 5,266 patients who had received radiation treatment to the head and neck, 1,476 were examined for risk factors in the development of thyroid carcinoma. The patients represented 84.6% of the group who received radiation to the tonsil-nasopharynx area, which had the highest (31.1%) incidence of nodular thyroid disease. The other groups received radiation to the thymus, cervical nodes, chest, or other miscellaneous areas. Nodular thyroid disease was more frequent in women than in men, but the incidence of cancer in these patients was similar. The calculated risk of thyroid carcinoma was 4.6 carcinomas/ 10^6 persons/rad/yr. There were no distinctions between benign and malignant tumors with respect to age at treatment, latency, or total radiation dose. The incidence of new tumors appeared to increase for at least 32 yr, but a study of patients with previously detected tumors suggests a peak latency of 25 yr. (3 refs.)

77-6892 Carcinoma of Vagina 10 or More Years Following Pelvic Irradiation Therapy. (Eng)

Pride, G. L. (Dept. Obstetrics and Gynecology, Loyola Univ. Medical Center, 2160 S. First Ave., Maywood, IL 60153); Buchler, D. A. *Am J Obstet Gynecol* 127(5): 513-517; 1977.

The records of 4,238 patients with gynecological malignancies treated between 1956 and 1974 were reviewed to select patients that developed cancer of the cervix or vagina 10 yr or more after radiation therapy. Sixteen patients (av age 57.3 yr) were identified: 3 had squamous carcinoma in situ and 13 had invasive squamous cancer involving the upper vagina. The mean time interval between primary irradiation and discovery of the neoplasm was 18.3 yr. Nine patients with primary invasive carcinoma had no adjacent cervical involvement; another four patients originally classified as recurrent cervical carcinoma had histological evidence of a new primary in the upper vagina adjacent to an irradiated cervix. All patients receiving radiation therapy to the vaginal epithelium should have Pap smears at frequent intervals to detect vaginal neoplasia or recurrent cervical cancer. (16 refs.)

77-6893 Chronic Myelogenous Leukemia Developing after Irradiation. (Eng) Shimaoka, K. (Dept. Medicine B, Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY 14263). In: *Radiation-associated Thyroid Carcinoma*. Degroot, L. J.; Frohman, L. A.; Kaplan, E. L.; Refetoff, S., eds. (New York: Grune & Stratton): 539 pp.; 485-491 pp.; 1977.

Of 327 patients with chronic myelogenous leukemia (CML, all seen between 1914 and 1975), 29 (14 women, 15 men) were found to have a history of radiation exposure. For these patients, the mean age at diagnosis of CML was 46.2 yr, and the mean duration between exposure and CML diagnosis was 14.6 yr. Sixteen patients had been treated for malignant diseases: 4 of these patients received radium, 2 radioisotopes, and 10 conventional radiation therapy. The other 13 received radiation for nonmalignant conditions, 7 in utero. All 29 patients probably had radiation-induced CML. (19 refs.)

77-6894 Haemangiosarcoma Following Irradiation of a Haemangioma of the Face (Case Report). (Eng) Ward, C. M. (Wessex Centre Plastic and Maxillo-Facial Surgery, Odstock Hosp., Salisbury, Wiltshire, England SP8BJ); Buchanan, R. *J Maxillofac Surg* 5(3): 164-166; 1977.

A 22-yr-old man who died of metastatic hemangiosarcoma had been irradiated at the age of 5 mo with 1,340 rads to the skin surface for a facial capillary hemangioma. The hemangioma had resolved rapidly at the expense of a nonfunctioning parotid, atrophic skin changes, and impaired maxillary and mandibular growth. At age 18, an irregular, firm nodule developed in front of the patient's left ear. It was excised, but it recurred several months later, requiring further excision. At age 20, another tumor that extended into the sc fat was excised; there was no evidence of metastases. A recurrence 3 mo later resulted in extensive resection; an extension of the tumor into the mastoid bone was irradiated with high-energy electrons (4,500 rads in 10 fractions). Another recurrence 9 mo later was treated with 6,250 rads in 25 fractions, with tumor regression. Six months later, bronchoscopic biopsy indicated the metastases, and the patient died 5 mo later. The behavior of the tumor suggested that it resulted from the radiation treatment. (14 refs.)

77-6895 Lung Carcinoma after Radiotherapy and Chemotherapy for Hodgkin's Disease. (Eng) Matthey, R. A. (Pulmonary Div., Dept. Medicine, Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, CT 06510); Zorn, S. K.; Mitchell, M. S.; Papac, R. J. *Thorax* 32(5): 628-631; 1977.

Two men, aged 29 and 41 yr, developed carcinoma of the lung after radiotherapy (4,500 and 3,500 rads initially, and 4,000 and 3,400 rads for recurrence, respectively) and chemothera-

py for nodular sclerosing Hodgkin's disease (NSHD). The carcinomas developed in the previous radiation port 4 and 6 yr, respectively, after successful therapy. It is concluded that intensive radiotherapy can cure NSHD but cause a second malignancy. (6 refs.)

77-6896 Quantitative Comparison of Environmental Carcinogens: Chemical Versus Ionizing Radiations (Meeting Abstract). (Eng) Latarjet, R. (Institut du Radium-Biologie, 26 rue d'Ulm, 75005 Paris, France); Moustacchi, E.; Averbeck, D.; Markovits, P. In: *Fourth Meeting of the European Association for Cancer Research, 13th-15th September, 1977*. International Agency for Research on Cancer. (Lyon, France): p. 67; 1977. (no refs.)

77-6897 Blastomogenesis in Mice by Prenatal Exposure to N-Nitrosoethylurea and Postnatal X-Ray Irradiation. (Rus) Napalkov, N. P. (Lab. Experimental Tumors, N. N. Petrov Scientific Res. Inst. Oncology, USSR Ministry Public Health, Leningrad, USSR); Tomatis, L.; Likhachev, A. Ia.; Kolodin, V. I. *Vopr Onkol* 23(4): 49-57; 1977.

The blastomogenic effects of intrauterine exposure to N-nitrosoethylurea (NEU) with and without postnatal x-ray irradiation were studied in male and female BALB/c mice. The spontaneous tumor incidence in untreated controls was 28/63. Tumors occurred in 33/71 irradiated offspring of untreated mothers; the offspring had received a single x-ray dose of 150 R in 6 min at age 100 days. Tumor incidence was 60/72 in the irradiated offspring of mothers who had received a single 20-mg dose of NEU ip 24-72 hr before delivery. The tumors included 16 pulmonary adenomas and 44 pulmonary adenocarcinomas. Postnatal x-radiation enhanced the transplacental blastomogenic effect of NEU and increased the incidence of pulmonary neoplasms, mainly adenocarcinomas. In another group, the male and female offspring of NEU-treated mothers lived together; tumor incidence was 19/31 among males (18 lung tumors, 1 other tumor) and 28/38 among females (24 lung tumors, 6 mammary gland tumors, 5 other tumors). In a second control group, in which untreated females and males from untreated mothers lived together, the incidence of mammary gland tumors among the females was 5/38, or 5/14 tumors. These findings indicate that gestation and feeding of offspring in groups of females and males living together increase the incidence of mammary gland tumors regardless of prenatal exposure to NEU and postnatal x-irradiation. (24 refs.)

77-6898 Radiosensitivity of Lymphocyte Stimulation. Part 3: Lymphocyte Stimulation, a Model for

Radiobiological Studies of Stimulated Proliferation--Conclusions from Experimental Results. (Ger) Renner, H. (Abteilung Strahlentherapie, Stadt. Krankenanstalten, Flurstrasse 17, 8500 Nurnberg, W. Germany). *Strahlentherapie* 153(3): 171-177; 1977.

The high radiosensitivity of small lymphocytes may be due to their low metabolic activity and limited repair capacity. Stimulated differentiated lymphocytes are less radiosensitive. In vitro, rapidly and spontaneously proliferating lymphocytes are most sensitive during the S phase, but the G₁ phase is relatively radioresistant. DNA synthesis is slightly stimulated; the radiation effect manifests itself by a block of G₂ and delayed mitosis. The next cell cycle seems to be normal after irradiation during G₂. Cell systems with stimulated proliferation, however, are radiosensitive during the G₁ phase, and DNA synthesis is delayed or blocked. The phase of DNA synthesis that is radiosensitive is during the production of DNA-synthesizing enzymes, especially thymidine kinase and DNA polymerase. The number of proliferating cells is reduced by a block of G₁ during the first cell cycle and by a block of G₂ and inhibition of mitosis during the second and subsequent cell cycles. (no refs.)

77-6899 **Correlation Between Mast Cell Content and Neoplastic Proliferation of the Mammary Gland Epithelium.** (Rus) Strel'tsova, V. N. (No affiliation given); Pavlenko-Mikhailov, Iu. N. *Vopr Onkol* 23(6): 53-57; 1977.

The relationship between mast cell content of the mammary gland stroma and γ radiation-induced proliferation of the mammary gland epithelium was studied in 77 random-bred female albino rats irradiated with 200 R at a dose rate of 457.8 R/min. On day 180 after irradiation, 32.4% of the animals showed hyperplasia and 10% had benign breast tumors; on day 360, 66% had benign tumors. Eight percent had malignant tumors (adenocarcinomas, ductal carcinoma, and mamillary carcinoma) on day 270. On day 540, 38/50 animals that survived 180 days had benign (adenomas, adenofibromas, mixed) and malignant tumors. Progressive proliferation of the stromal epithelium and an increase in mast cells were seen during the latency period (their first 180 days); the mast cell count reached its max on day 180. A subsequent reduction in mast cells between days 180 and 270 reflected stabilization of the benign process and resistance of the rat to the progression of neoplasia. The mast cell count increased again after day 270, reaching another max on day 450. The period from days 360 to 450 corresponded to the time of malignant transformation of the benign tumors and to an increase in the number of pituitary gland tumors. (22 refs.)

77-6900 **ESR Study of the Effect of Visible Light on γ -irradiated DNA and Its Constituents at 77**

K. (Eng) Kominami, S. (Dept. Environmental Sciences, Faculty Integrated Art and Science, Hiroshima Univ., Hiroshima 730, Japan); Wee, V. T.; Riesz, P. *Radiat Res* 69(2): 213-222; 1977.

Electron spin resonance was used to study the effect of visible light (410-550 nanometer (nm)) on radical composition and concentration in solid DNA (salmon sperm DNA) and DNA constituents previously γ -irradiated at -196 C in the dark in vacuo. For DNA, adenine, cytosine, and guanine, $\geq 70\%$ of the radicals were removed by illumination at -196 C; for thymine and 2'-deoxy-D-ribose, about 20% were removed. The decrease of the radical concentration for the corresponding nucleosides was smaller. For thymidine, the radical concentration was unchanged by illumination. The combined effects of thermal annealing and illumination on γ -irradiated DNA were also investigated. Quantitative results were obtained for radical survival after prolonged illumination, after illumination plus storage at room temperature for 1 day, and after storage in the dark at room temperature for 1 day. The radical concentration after illumination at -196 C plus storage at room temperature was equal to the radical concentration after storage at room temperature in the dark. This result contrasts that obtained on thermal annealing after illumination of DNA constituents, and it suggests that the mechanism for thermal radical decay might be different for the high-mol-wt polymers. (30 refs.)

77-6901 **Radiation-induced Nerve Root Degeneration and Hypertrophic Neuropathy in the Lumbosacral Spinal Cord of Rats: The Relation with Changes in Aging Rats.** (Eng) van der Kogel, A. J. (Radiobiological Inst. TNO, 151 Lange Kleiweg, Rijswijk, Netherlands). *Acta Neuropathol (Berl)* 39(2): 139-145; 1977.

At 3 mo of age, WAG/Rij rats were irradiated with 300-kilovolt x-rays on the lumbar region of the spinal column, at doses below the level causing paralysis due to radiation radiculomyelopathy. At 8-9 mo post-irradiation, the ventral nerve roots of the cauda equina had degenerated. Three stages were distinguishable: (1) demyelination and proliferation of Schwann cells; (2) local swelling of ventral nerve roots, with concentric layers of Schwann cells resembling hypertrophic neuropathy; and (3) malignant schwannoma invading the roots and spinal cord. It is concluded that the degenerative and proliferative lesions represent three consecutive stages of slowly progressive lesions. The ventral nerve root degeneration (1st stage) is similar to that observed in aging, unirradiated rats normally developing at the age of 18-20 mo. (12 refs.)

77-6902 **The Repair of X-Ray-induced Chromosomal Damage in Trisomy 21 and Normal Diploid Lymphocytes.** (Eng) Countryman, P. I. (Dept. Biology, York

univ., Downsview, Ontario M3J 1P3, Canada); Heddle, J.; Crawford, E. *Cancer Res* 37(1): 52-58; 1977.

The possibility that the increased frequency of x-ray-induced chromosome aberrations in trisomy 21 patients (Down's syndrome) is due to a defect in the rejoining system that repairs chromosome breaks was investigated. The time required for the rejoining (repair) of chromosome breaks was measured in lymphocytes from 5 Down's syndrome (4 trisomy 21 and 1 D/G translocation partial trisomy 21) donors, from 1 monosomy 21 donor, and from 5 diploid donors. The rejoining time was reduced in the Down's syndrome lymphocytes compared with the normal diploid and monosomy 21 lymphocytes. Thus, the repair of chromosome breaks occurred more rapidly in Down's syndrome cells than in normal cells. A mechanism is proposed by which reduced rejoining times would increase aberration frequencies as a consequence of competition between a (hypothetical) error-free repair system and the error-prone repair system that generates chromosomal aberrations. The alteration in the rejoining of chromosome aberrations may underlie the increased susceptibility of Down's syndrome patients to leukemia. (32 refs.)

77-6903 Repair of Ultraviolet Light Damage in a Variety of Human Fibroblast Cell Strains. (Eng) Lehmann, A. R. (Medical Res. Council Cell Mutation Unit, Univ. Sussex, Falmer, Brighton, BN1 9QG, England); Kirkbell, S.; Arlett, C. F.; Harcourt, S. A.; de Weerd-Kastelein, E. A.; Keijzer, W.; Hall-Smith, P. *Cancer Res* 37(3): 904-910; 1977.

Repair mechanisms and cell survival were studied in xeroderma pigmentosum (XP) human fibroblast strains from all five complementation groups, several XP variant strains, and fibroblasts from patients who were sensitive to sunlight or multiple cancers, and from patients who had hereditary disorders and a possible sensitivity to radiation or chemicals. A defect in postreplication repair was found in five variants (XP7TA, XP3ORO, XP4BE, XP943OLO, and XP1NY), and a less severe defect was found in excision-defective XP cells in complementation groups A, B, C, and D. Group E and all other cell strains studied showed a response not significantly different from that of normal cells. Excision repair was defective only in XP cells. UV cell survival characteristics indicated that the most sensitive cells were those from the excision-deficient XP's and from a sun-sensitive child; the latter had no measurable defect in either excision or postreplication repair. The remainder of the survival curves lay between those of normal cells and the slightly more sensitive excision-proficient XP variant XP3ORO. Only XP3ORO and XP7TA survival was influenced by caffeine treatment (75 µg/ml). (47 refs.)

77-6904 Interaction of Restoration Processes in UV Irradiated *Escherichia coli* Cells. (Eng) Sed-

liakova, M. (Slovak Acad. Sciences, Cancer Res. Inst., Dept. Molecular Genetics, Mlynske Nivy 59, Bratislava, Czechoslovakia); Brozmanova, J.; Masek, F.; Slezarikova, V. *Photochem Photobiol* 25(3): 259-264; 1977.

Cell survival and DNA synthesis were studied in UV-irradiated *Escherichia coli* B/r *her+* and *her-* cells (dimer excision-proficient and excision-deficient cells, respectively). In exponentially growing *her+* cells irradiated at 30 joules/min, dimers were almost completely excised and cell survival was approx 3%. Cell survival was similar in irradiated *her+* cells prestarved for amino acids and thymine, but two-thirds of the dimers remained unexcised. They could be detected in hybrid DNA consisting of parental and daughter chains. After UV exposure, exponentially growing *her-* cells produced unexcised dimers in amounts comparable to those produced by the prestarved *her+* cells. However, cell survival was only 0.02%. Despite the difference in their dimer content, irradiated growing and prestarved *her+* cells replicated similar amounts of DNA, which formed well-defined hybrid peaks. In the *her-* cells, the amount of replicating DNA was too low to form a detectable hybrid peak. The results indicate that *her+* cells can tolerate substantially higher amounts of unexcised lesions than *her-* cells. (26 refs.)

77-6905 Time of Appearance and Histology of Tumors Induced in the Dorsal Skin of C3Hf Mice by Ultraviolet Radiation from a Mercury Arc Lamp. (Eng) Spikes, J. D. (Dept. Biology, Univ. Utah, Salt Lake City, UT 84112); Kripke, M. L.; Connor, R. J.; Eichwald, E. J. *J Natl Cancer Inst* 59(6): 1637-1643; 1977.

The time course of skin tumor induction was determined in hair-clipped inbred agouti C3Hf mice irradiated three times per week with a medium-pressure quartz-mercury lamp. Four different UV doses were used: 6.5×10^6 , 2.2×10^6 , 0.65×10^6 , and 0.22×10^6 ergs/cm²/wk. In the three groups given the highest doses, no ear tumors were observed by the time each animal had developed at least one back tumor. No tumors were found in the animals receiving the lowest UV dose. In the group receiving the highest dose, males developed tumors earlier than females; this trend continued in the lower dose groups. Many tumors that developed in the back skin were well-differentiated squamous cell carcinomas. Others were less well-defined, so the cell of origin was difficult to determine. The squamous cell carcinomas predominated at the lower doses. (27 refs.)

77-6906 Endonuclease from *Escherichia coli* That Acts Specifically upon Duplex DNA Damaged by Ultraviolet Light, Osmium Tetroxide, Acid, or X-rays. (Eng) Gates, F. T. (Lab. Immunology and Immunochemistry, Rockefeller Univ., New York, NY 10021); Linn, S. *J Biol Chem* 252(9): 2802-2807; 1977.

An *Escherichia coli* endonuclease that acts on UV-irradiated DNA at a photoproduct site other than thymidine dimers was isolated and characterized. Sedimentation analysis suggested a mol wt of 27,000 if the protein is assumed to be spherical. The enzyme does not require Mg^{+2} for activity, is active in the presence of 4 mM EDTA, is inhibited by 1 M NaCl, and is inhibited by transfer RNA. It has a pH optimum of approx 7. The enzyme nicks duplex DNA exposed to OsO_4 , x-rays, or acid, but it does not react with undamaged DNA or irradiated single-stranded DNA. There was a rough correlation between the number of endonuclease-sensitive sites and the number of alkali-labile sites in x-irradiated and heat/acid-treated substrates, but most UV-irradiated and OsO_4 -treated sites were alkali-stable. This indicates that the enzyme can act at sites other than apurinic/apyrimidinic sites. No exonuclease, DNA N-glycosidase, or RNase activities were detected. The incisions created by the endonuclease contain 5'-phosphate termini. These findings suggest that this endonuclease is the same as *E. coli* endonuclease III. (28 refs.)

- 77-6907 **Formation of a Thymine Photoproduct in Transforming DNA by Near Ultraviolet Irradiation.** (Eng) Cabrera-Juarez, E. (Biology Dept., Brookhaven Natl. Lab., Upton, NY 11973); Setlow, J. K. *Biochem Biophys Acta* 457(2): 315-322; 1977.

A highly purified preparation of thymine-labeled transforming DNA from *Hemophilus influenzae* was irradiated at 334 and 365 nanometers (nm), and the resulting photoproduct was identified by chromatography and scintillation counting as a thymine photoproduct. The photoproduct was soluble in water and in ethanol and was resistant to 254 nm radiation. The failure of irradiation at 254 nm to change the chromatographic properties of the photoproduct indicates that it is not a thymine-containing cyclobutane dimer. The photoproduct has properties similar to those of the spore photoproduct 5-thyminyl-5,6-dihydrothymine but it is not certain whether or not the two photoproducts are different or the same. Inactivation of the DNA transforming activity and the amount of photoproduct appear to be correlated, but mutation was unrelated to photoproduct concentration. Thus, the photoproduct is more likely to affect the oxygen-independent inactivation of transforming DNA rather than its mutagenesis; ie, it is more likely to be a lethal rather than a mutagenic lesion. (17 refs.)

- 77-6908 **Role of Acoustic Stress in the Development of Polyoma Virus-induced Tumors in Immunized Golden Hamsters.** (Fre) Serafino, X. (Institut J. Paoli et I. Calmettes, 232, boulevard de Sainte-Marguerite, 13273 Marseille Cedex 2, France); Extremet, J.; Fresco, R.; Meyer, G. *C R Acad Sci [D] (Paris)* 285(5): 627-629; 1977.

The effect of ultrasonic stress (100 kilocycles/sec for 5 min, bid for 4 wk) on the protective action of polyoma virus vac-

cine (3×10^7 plaque-forming units) was studied in golden hamsters following sc transplantation of polyoma virus-induced C.T.54 tumor cells (25,000 cells/animal, 5 times the median tumor dose). The animals were examined for tumors on days 24 and 42. Group 1 was immunized before transplantation without acoustic stress; tumor induction on both dates was 0/16. Group 2 was immunized and subjected to stress simultaneously, before tumor transplantation; tumor incidence was 3/16 on day 24, 8/16 on day 42. Group 3 was immunized and stressed twice, once before and once during tumor transplantation; tumor incidence was 0/16 on day 24, 2/16 on day 42. Group 4 was immunized and then exposed to ultrasound without tumor transplantation; none of the 16 animals developed a tumor. Group 5 received tumor graft only; tumor incidence was 9/16 on day 24, 16/16 on day 42. The findings indicate that exposure to ultrasound during immunization markedly decreased the protective effect of the virus. (2 refs.)

- 77-6909 **Studies on the Preneoplastic Stage of Foreign Body Tumorigenesis (Meeting Abstract).** (Eng.) Mozer, B. J. (Univ. Minnesota, Minneapolis, MN 55455). *Diss Abstr Int [B]* 38(3): 1146; 1977. (no refs.)

- 77-6910 **Foreign-Body Tumors of Mice: Strain and Sex Differences in Latency and Incidence.** (Eng) Brand, I. (Dept. Microbiology, Univ. Minnesota Medical Sch., Minneapolis, MN 55455); Buoen, L. C.; Brand, K. G. *J Natl Cancer Inst* 58(5): 1443-1447; 1977.

Sarcomas were induced by sc implantation of unplasticized polyvinyl chloride acetate films in female and male mice of strains AKR/J, BALB/cJ, BALB/cWat, CBA/H and CBA/H-T6, C3H/HeJ, C57BL/10ScSn, C57BL/6J-bgJ, C57BR/cdJ, DBA/1J, I/LnJ, LP/J, SJL/J, X/Gf, 129J, and hybrids (CBZ/H-T6 x AKR/J) F_1 , (C57BL/10ScSn x CBA/H or CBA/H-T6) F_1 , and (C57BL/6J-bgJ x C57BL/6J) F_1 . The strains and sexes showed marked differences in tumor incidence and mean latency. Crucial information was obtained for the selection of appropriate mouse strains for studies of interrelationships between genotypes, defined somatic properties, and the multifactorial process of foreign-body tumorigenesis. (no refs.)

- 77-6911 **Carcinogenicity of Fibrous Glass: Pleural Response in the Rat in Relation to Fiber Dimension.** (Eng) Stanton, M. F. (Lab. Pathology, NCI, NIH, Public Health Service, U.S. Dept. Health, Education, and Welfare, Bethesda, MD 20014); Layard, M.; Tegeris, A.; Miller, E.; May, M.; Kent, E. *J Natl Cancer Inst* 58(3): 587-603; 1977.

Seventeen different fibrous glasses induced different incidences of malignant mesenchymal neoplasms when implanted (standard dose of 40 mg fibers suspended in gelatin and coated on flat pledgets) in the pleura of female Osborne-Mendel rats for > 1 yr. The carcinogenicity of the fibers correlated with their dimensional distribution. Fibers ≤ 1.5 micrometers (μm) in diameter and > 8 μm in length yielded the highest probability of pleural sarcomas, and probability trends suggested that sarcoma incidence increased with increasing lengths of fibers with diameters < 1.5 μm . Morphologic observations indicated that fibers ≤ 8 μm in length were inactivated by phagocytosis. In fibers > 8 μm long, the correlation of carcinogenicity with increasing length was difficult to explain. It may be related to the amount of fiber surface free of phagocytic activity and to the amount of collagen on the fiber surface. The results support the concept that the carcinogenicity of fibers depends on dimension and durability rather than on physicochemical properties. (32 refs.)

77-6912 Release of Enzymes of Alveolar Macrophages during the Phagocytosis of Chrysotile Fibers (Meeting Abstract). (Fre) Jaurand, A. C. (Service de Pneumologie, Centre Hospitalier Intercommunal, 40, avenue de Verdun, 94010 Creteil, France); Bignon, J.; Magne, L. *Pathol Biol (Paris)* 25(7): 469; 1977. (3 refs.)

77-6913 Experimental Study of the Effects of Chrysotile Asbestos on the Biochemical Microenvironment of the Pulmonary Alveolus. (Eng) Warnet, L. M. (Laboratoire de Toxicologie, Faculte de Pharmacie, Universite Rene-Descartes, Paris, France); Oblin, A.; Jaurand, M. C.; Bignon, J.; Claude, J. R.; Truhaut, R. *Proc Eur Soc Toxicol* 18: 324-325; 1977.

The action of chrysotile asbestos and SO_2 -absorbed chrysotile on the rabbit pulmonary alveolus was investigated. Both compounds significantly increased the soluble protein content of the 100,000 x g supernatant from the alveolar washings. An analysis of the lecithins showed that both substances increased the level of unsaturated fatty acids. (no refs.)

77-6914 Mortality of a Cohort Exposed to Chrysotile Asbestos. (Eng) Weiss, W. (Div. Occupational Medicine, Dept. Medicine, 6401 New Coll. Building, Hahnemann Medical Coll. and Hosp., 15th and Vine Sts., Philadelphia, PA 19102). *J Occup Med* 19(11): 737-740; 1977.

A 30-yr historical cohort mortality study was made of 264 men who worked in a chrysotile asbestos products factory for ≥ 1 yr in the period 1934-1945 and who were alive January 1, 1945. The follow-up was 94% complete. The overall standardized mortality ratio (SMR) was only 0.61; the SMR was 0.75 for all carcinomas, 0.93 for lung cancer, and 1.05 for gastrointestinal cancer. Two men died of asbestosis. The overall SMR was higher for men who worked ≥ 5 yr than for men who worked 1-5 yr, but the age-adjusted mortality rates were the same. For asbestos-related diseases, the differences in work duration had no effect on mortality. The data indicate that the hazard of occupational exposure to chrysotile asbestos is minimal. (15 refs.)

See also:

*(Rev.): 77-6627, 77-6628, 77-6629, 77-6630, 77-6631, 77-6632, 77-6633, 77-6634, 77-6635, 77-6636, 77-6637.

*(Chem.): 77-6674, 77-6675, 77-6736, 77-6746, 77-6808.

*(Viral): 77-6939, 77-7002.

*(Immun.): 77-7039.

*(Path.): 77-7098, 77-7135, 77-7138.

*(Epid.-Biom.): 77-7172.

VIRAL CARCINOGENESIS

- 77-6915 **Oncornavirus-induced Sarcoma Formation Obscured by Rapid Development of Lethal Leukemia.** (Eng) Graf, T. (Max-Planck-Institut für Virusforschung, Biologisch-Medizinische Abteilung, Tübingen, W. Germany); Fink, D.; Beug, H.; Royer-Pokora, B. *Cancer Res* 37(1): 59-66; 1977.

Inoculation of chicks with avian erythroblastosis virus (AEV) strain caused a high incidence of leukemia and death of most of the chicks within 2 wk. This virus is defective for replication and transforms bone marrow cultures and chick embryo fibroblasts in vitro. Injection of transformed AEV cells negative for virus production into newborn chicks induced the formation of sarcomas only, but cells superinfected with helper virus induced the formation erythroblastosis in addition to sarcomas. The helper virus alone caused neither sarcomas nor erythroblastosis during the experimental period. It is hypothesized that AEV-induced erythroblastosis develops more rapidly than AEV-induced sarcomas and that chicks receiving iv injections die of leukemia before sarcomas become detectable. The observation that chicks receiving im injections of AEV developed sarcomas at the injection site strongly supports this concept. Most chicks injected also developed erythroblastosis, but at a later date than those injected iv. The data also suggest that the erythroblastosis induced by AEV does not suppress the formation of sarcomas in the same animal. (11 refs.)

- 77-6916 **Infidelity of DNA Synthesis by Temperature-sensitive DNA Polymerases from RNA Tumor Viruses.** (Eng) Weymouth, L. A. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111); Loeb, L. A. *Biochem Biophys Acta* 478(3): 305-315; 1977.

The role of reverse transcriptase in base-selection was analyzed using mutant DNA polymerases from RNA tumor viruses. Three temperature-sensitive DNA polymerases from avian sarcoma viruses and a wild-type DNA polymerase from an avian leukosis virus were assayed for the inaccuracy in copying homopolymers in vitro. With poly(A)-oligo(dT) as a template, the frequency of incorporation of the noncomplementary nucleotide, deoxycytidine monophosphate into the poly(dT) product varied from 1 in 235 to 1 in 276. With poly(C)-oligo(dG) as template, the incorporation of deoxy-AMP into poly(dG) varied from 1 in 875 to approx 1 in 1,700. Analyses of the polynucleotide products of the reaction by equilibrium density centrifugation and digestion with snake venom phospho-

diesterase indicated that the noncomplementary nucleotides were incorporated in phosphodiester linkage and distributed throughout the length of the product. With poly(A) and poly(C) templates, the incorporation rate of both complementary and noncomplementary nucleotides by each mutant DNA polymerase was temperature-sensitive compared with that of wild-type DNA polymerase. These data demonstrate that the polymerase itself catalyzes the incorporation of both complementary and noncomplementary nucleotides. Partial heat denaturation of the mutant polymerases did not change the fidelity of copying poly(A). With poly(C) as template, however, partial heat inactivation increased the error frequency of one of the mutant polymerases and decreased the error frequency of another. These results suggest that mutations studied may alter base discrimination by the polymerase in a template-dependent manner. (31 refs.)

- 77-6917 **Avian Tumour Virus Interactions with Chicken Fibroblast Membranes: Partial Characterization of Initial Attachment Site Activity.** (Eng) Moldow, C. F. (Dept. Medicine, Univ. Minnesota Medical Sch., Minneapolis, MN 55455); Volberding, P.; McGrath, M.; Lee, J. *J Gen Virol* 37(2): 385-398; 1977.

When chicken embryo fibroblasts (CEF) are exposed to trypsin, the cell surface components, including the initial attachment site for avian tumour viruses (ATV), are solubilized. This soluble attachment site activity appeared to interact directly with the ATV in vitro, thus interfering with the binding of at least two ATV subgroups (Rous associated viruses RAV-1 and RAV-2) to both intact CEF and CEF plasma membranes. A result of this interaction in vitro was reduced ATV infectivity, demonstrated by the reduced transforming capacity of RAV-1. (24 refs.)

- 77-6918 **Oncogenicity of Avian Leukosis Viruses of Different Subgroups and of Mutants of Sarcoma Viruses.** (Eng) Purchase, H. G. (Natl. Program Staff, Agricultural Res. Station, Beltsville, MD 20705); Okazaki, W.; Vogt, P. K.; Hanafusa, H.; Burmester, B. R.; Crittenden, L. B. *Infect Immun* 15(2): 423-428; 1977.

The oncogenicity of leukosis viruses of subgroups A-G was determined in chickens susceptible to virus infection and to the development of lymphoid leukosis (LL) tumors. All subgroup A viruses and the subgroup B virus tested produced

high incidence of LL and other related neoplasms. Viruses of subgroup C and a Rous-associated virus (RAV-61) of subgroup F produced a low level of LL. The RAV-50 of subgroup D produced osteopetrosis. In these tests, the viruses of subgroups E and G and one virus of subgroup F were not pathogenic, possibly because infection was not established in the chickens, the chickens were not susceptible to tumor development by these viruses, or the viruses lacked oncogenicity. All temperature sensitive mutants of Rous sarcoma virus produced sarcomas, but the incidence varied. One nontransforming mutant produced sarcomas, and the other three tested produced LL. All three mutants that cause cells to grow in colonies in agar produced a high incidence of sarcomas. Thus, sarcoma viruses, by back-mutation, may lose their ability to transform cells in vitro, to make cells grow in agar colonies, or to induce sarcomas in vivo, although they retain the ability to produce LL. Conversely, leukosis viruses may be changed into viruses that transform cells in vitro and produce sarcomas in vivo by suitable passage in chicks. (31 refs.)

77-6919 Purification of DNA Complementary to the *env* Gene of Avian Sarcoma Virus and Analysis of Relationships among the *env* Genes of Avian Leukosis-Sarcoma Viruses. (Eng) Tal, J. (Dept. Microbiology, Univ. California, San Francisco, CA 94143); Fujita, D. J.; Kawai, Y.; Varmus, H. E.; Bishop, J. M. *J Virol* 21(2): 497-505; 1977.

DNA complementary to nucleotide sequences encoding part or all of the *env* genome for both subgroup A avian sarcoma virus (ASV) (cDNA_{AgpA}) and subgroup C ASV (cDNA_{AgpC}) was isolated, and the relationships among nucleotide sequences encoding the *env* genes of different viral strains were determined. The genetic complexity of cDNA_{AgpA} (approx 1000 nucleotides) was sufficient to represent the entire deletion and most or all of the *env* cistron. The deletions in *env* of Bryan and rdNY8SR virus overlap, and cDNA_{AgpA} represents nucleotide sequences common to both deletions. No overlap was detected between deletions in *env* and deletions in the adjacent viral gene *src*. The specificity of cDNA_{AgpC} for the deletion in *env* was the same as that of cDNA_{AgpA}. Laboratory stocks of viral subgroups A, B, C, D, and E did not contain detectable amounts of *env* deletions when tested by molecular hybridization, indicating that segregation of deletions in *env* is less frequent than segregation of deletions in *src*. Extensive homology was noted in the sequences coding for the *env* genes of virus strains indigenous to chickens (subgroups A-E). In contrast, viruses obtained from pheasant cells (subgroups F and G) have *env* genes with little or no relationship to *env* genes of chicken viruses. Thus, viruses from subgroup F could have arisen by recombination between an avian sarcoma virus and viral genes in the genome of ring-necked pheasants; subgroup G may be endogenous to golden pheasants. (25 refs.)

77-6920 Major Phosphoprotein of Avian Sarcoma Virus: Peptide Analysis of the Variously Charged Spe-

cies. (Eng) Hayman, E. G. (Dept. Pathology, Univ. Southern California Sch. Medicine, Los Angeles, CA 90033); Pal, B. K.; Lai, M. M.; Roy-Burman, P. *Biochem Biophys Res Commun* 78(4): 1156-1161; 1977.

The 19,000-dalton phosphoprotein (pp19) of avian sarcoma virus strain B77, isolated by guanidine-agarose chromatography from secondary chicken embryo fibroblast-infected cells, was subjected to peptide analysis. It was resolved into multiple species in separation techniques based on ionic charge differences; ie, by polyacrylamide gel electrophoresis under 5.25 M urea denaturing conditions. Diethylaminoethyl cellulose was used to separate the highly and lowly phosphorylated species. The latter was only loosely bound to the column, but the former adhered tightly to the column. Peptide maps of these species revealed that they are similar. Thus, the multiple phosphorylated species of pp19 originate from the differential phosphorylation of a single major polypeptide. (12 refs.)

77-6921 Integration of Avian Sarcoma Virus DNA Sequences in Transformed Mammalian Cells. (Eng) Collins, C. J. (Dept. Microbiology, Univ. Virginia Medical Sch., Charlottesville, VA 22901); Parsons, J. T. *Proc Natl Acad Sci USA* 74(10): 4301-4305; 1977.

DNA from six avian sarcoma virus (ASV)-transformed mammalian cell lines was digested with the restriction endonucleases *EcoRI*, *Xho I*, or *Sal I*, fractionated by agarose gel electrophoresis, transferred to nitrocellulose filter strips, and hybridized with specific ASV³²P-complimentary DNA (cDNA) probes. DNA from all the ASV-transformed cell lines yielded three common virus-specific DNA fragments (2.4, 1.8, and 1.3 x 10⁶ daltons) upon cleavage with *EcoRI*. *Xho I* appeared to cleave at least once within the integrated provirus, and it yielded a common fragment of 3.3 x 10⁶ daltons as well as a second virus-specific DNA fragment whose size varied from 4.0 to 5.0 x 10⁶ daltons in the different transformed cell lines. *Sal I* did not cleave within the provirus, and it yielded a single major virus-specific fragment of about 11 x 10⁶ daltons in all transformed lines examined. The cDNA probes showed that the 1.8 x 10⁶-daltons *EcoRI* fragment contains sequences homologous to the 3' end of the viral RNA as well as to the *src* region of the viral genome. These studies demonstrate that the same region on the ASV genome is utilized for provirus integration in different ASV-transformed cell lines. (21 refs.)

77-6922 Translation of 35S and of Subgenomic Regions of Avian Sarcoma Virus RNA. (Eng) Purchio, A. F. (Dept. Microbiology and Immunology, Univ. California, Sch. Medicine, Los Angeles, CA 90024); Erikson, E.; Erikson, R. L. *Proc Natl Acad Sci USA* 74(10): 4661-4665; 1977.

Rabbit antiserum monospecific for an internal structural protein, p27, of avian sarcoma viruses (ASV) immunoprecipitated polypeptides with mol wt of 180,000 and 76,000 from cell-free reticulocyte lysates programmed by ASV 35S RNA and also from lysates of ASV-infected cells. In addition, the 180,000-mol wt protein was precipitated by antiserum raised against virion DNA polymerase, suggesting that it is a product of translation of the two genes nearest the 5' end of virion 35S RNA. The ability of subgenomic portions of virion RNA to program cell-free protein synthesis was also investigated. A 10S-12S poly(A)-containing fragment of RNA from both nondefective and transformation-defective ASV directed the synthesis of a 29,000-mol wt polypeptide immunologically unrelated to the group-specific antigen. A 20S-24S poly(A)-containing RNA from nondefective ASV directed the synthesis of a 60,000-mol wt polypeptide not found when a similar RNA preparation from transformation-defective ASV was translated, suggesting that it is the product of the ASV *src* gene. These results indicate that internal initiation sites for protein synthesis exist on the 35S RNA genome. (27 refs.)

- 77-6923 **Infectious DNA of Spleen Necrosis Virus Is Integrated at a Single Site in the DNA of Chronically Infected Chicken Fibroblasts.** (Eng) Battula, N. (McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI 53706); Temin, H. M. *Proc Natl Acad Sci USA* 74(1): 281-285; 1977.

The infectious DNA's of a number of avian leukosis-sarcoma viruses (Schmidt-Ruppin Rous sarcoma virus D, Bratislava strain 77 virus, and Prague Rous sarcoma virus C) and reticuloendotheliosis viruses [spleen necrosis virus (SNV), chick syncytial virus, reticuloendotheliosis virus (strain T), and duck infectious anemia virus] were digested with six nucleotide-specific restriction endonucleases, and the digests were tested for infectivity. All of the enzymes inactivated the viral infectivities except for *EcoRI*, which did not inactivate the infectivity of the DNA of SNV and chick syncytial virus. After digestion with *EcoRI*, the infectious DNA of SNV had a buoyant density in CsCl solution that was greater than the density of the high-mol-wt infectious viral DNA. The infectious *EcoRI*-digested SNV DNA from chronically infected chicken cells was a uniform size of 10 megadaltons, indicating that the infectious fragments were composed partly of host and partly of viral nucleotide sequences and that they were derived from a single site of integration. The infectious *EcoRI*-digested SNV DNA from acutely infected cells was heterogeneous in size (8-14 megadaltons), indicating multiple integration sites. These results are consistent with the hypothesis that cells that integrate infectious SNV DNA at a single site survive and multiply, whereas cells that integrate infectious viral DNA at additional sites either die or selectively lose or inactivate the DNA in the additional sites. (21 refs.)

- 77-6924 **New Procedure for the Direct Analysis of In Vitro Reverse Transcription of Rous Sarcoma Virus RNA.** (Eng) Darlix, J. L. (Departement de Biologie Molculaire, Universite de Geneve, 1211 Geneva 4, Switzerland); Bromley, P. A.; Spahr, P. F. *J Virol* 22(1): 118-129; 1977.

The concept that in vitro transcription of Rous sarcoma virus (RSV) RNA by avian myeloblastosis virus DNA polymerase renders the RNA progressively more sensitive to *Escherichia coli* RNase H digestion is the basis of a new procedure for the in situ analysis of this process. In vitro transcription products of ³²P-labeled RSV RNA are first treated with RNase H; the resistant fraction is then digested to completion with RNase T₁, and the oligonucleotides are analyzed by a fingerprint technique. By using the established order of these oligonucleotides along the RNA molecule, a comparison of the yields of each oligonucleotide, before and after transcription, allowed qualitative and quantitative in situ analyses of transcription. This new procedure showed that upon transcription of purified RSV RNA, DNA synthesis occurs mainly at three sites, one near the 5' end and two near the center of the subunit RNA molecule. Most of these RNA molecules are competent templates for limited transcription at these specific sites. Purified RSV 70S RNA contains a low-mol-wt DNA hybridized to a nucleotide sequence near the center of the subunit molecule. The low-mol-wt nucleic acid fraction extracted from purified RSV virions contains DNA that can hybridize to RSV 70S RNA; the virion DNA in such hybrids can function as a primer for an extensive in vitro reverse transcription. (22 refs.)

- 77-6925 **Decreased Adherence to the Substrate in Rous Sarcoma Virus-transformed Chicken Embryo Fibroblasts.** (Eng) Weber, M. J. (Dept. Microbiology, Univ. Illinois, Urbana, IL 61801); Hale, A. H.; Losasso, L. *Cell* 10(1): 45-51; 1977.

Cell-substrate adherence was examined in cultures of normal and Rous sarcoma virus-transformed chicken embryo fibroblasts by determining the number of cells that could be detached from the culture dish by a stream of medium. Transformed cells were significantly less adherent than their normal counterparts: 50%-70% of a transformed culture was detachable compared to 5%-15% of a normal culture. In cultures infected with a temperature-sensitive mutant of Rous sarcoma virus (RSV-T5) adherence changed promptly following a temperature shift. The transformation-specific decrease in adherence required new protein synthesis, but the restoration of adherence that occurred following a shift to the restrictive temperature could occur in the absence of new protein synthesis. Experiments using various inhibitors of macromolecule synthesis or function suggest the importance of microfilaments and microtubules in the changes in detachability. There was a positive correlation between levels of a large, external, transformation-sensitive cell-surface protein

ETS) and adherence when RSV-T5-infected cells were lifted in temperature or treated with the protease inhibitor N-ethylmaleimide. Normal levels of total LETS on the surface were neither necessary nor sufficient for normal adherence. Only a minor fraction of the surface LETS may be responsible for determining the adherence of these cells to the dish. (42 refs.)

6926 **Cellular Contaminants and Structural Proteins in Rous Sarcoma Virus (RSV): Study by Polyacrylamide Gel Electrophoresis.** (Fre) Connan, G. (Laboratoire de Medecine experimentale, U 112 de l'Institut national de la Sante et de la Recherche medicale, 11, place Marcelin Berthelot, 75231 Paris Cedex 05, France); Rabotti, G. F. *Cancer Res* [D] (Paris) 285(4): 463-465; 1977.

Polyacrylamide gel electrophoresis of the Rous sarcoma virus (RSV) from secondary chick embryo cultures revealed five bands with mol wts of $10\text{-}30 \times 10^3$ daltons and two bands with mol wts of $37\text{-}85 \times 10^3$ daltons, which correspond to the virus structural proteins. In addition, 13 to 18 bands of proteins of unknown origin were found in the highly purified RSV preparation. These proteins were similar to those isolated from the supernatant of noninfected cell cultures; ie, they are cellular contaminants. Fewer contaminating polypeptides were found in a myeloblastosis virus preparation purified from chicken plasma. (7 refs.)

6927 **Isolation from Normal and Rous Sarcoma Virus-transformed Chicken Fibroblasts of a Factor That Binds Glucose and Stimulates Its Transport.** (Eng) Lee, S. G. (Rockefeller Univ., New York, NY 10021); Schermann, F. *Proc Natl Acad Sci USA* 74(1): 163-167; 1977.

A glucose-binding factor was isolated from homogenates of normal and Rous sarcoma virus-transformed chick embryos by sucrose gradient centrifugation and Sephadex G-200 chromatography. The factor was bound to the membrane fraction, and this association was stronger in sarcoma cells than in confluent normal cells. In an assay of three determinants, the content of the binding factor increased 2.5-fold in the transformed cells, and it corresponded reasonably well to a fourfold increase in glucose uptake. The addition of 5 μM purified glucose-binding factor to quiescent cells increased glucose uptake sevenfold. The stimulation was an additive increment to the known stimulation by calf serum. (17 refs.)

6928 **Cellular Transformation and Differentiation. Effect of Rous Sarcoma Virus Transformation on Sulfated Proteoglycan Synthesis by Chicken Chondrocytes.** (Eng) Muto, M. (Natl. Inst. Radiological Sciences,

Anagawa, Chiba, Japan); Yoshimura, M.; Okayama, M.; Kaji, A. *Proc Natl Acad Sci USA* 74(10): 4173-4177; 1977.

Sulfate incorporation into sulfated proteoglycans by isolated chicken chondrocytes was inhibited up to 74% by transformation with Rous sarcoma virus (RSV). A similar inhibitory effect was observed upon acetate incorporation into chondroitin sulfate. Slower-sedimenting sulfated proteoglycans appeared after the viral transformation. The ratio of chondroitin 4-sulfate to chondroitin 6-sulfate in these sulfated proteoglycans was different from that of normal chondrocytes, but the chain lengths of the sulfated glycosaminoglycans produced by normal chondrocytes and transformed chondrocytes were not significantly different. Chondrocytes were also infected with a temperature-sensitive RSV mutant, ts LA24, which has a temperature-sensitive lesion in the transforming gene. Hyaluronic acid production by these cells was increased, and the slower-sedimenting sulfated proteoglycan was produced only at the permissive temperature. (17 refs.)

77-6929 **Transformation of Chicken Chondrocytes by Rous Sarcoma Virus.** (Eng) Okayama, M. (Dept. Microbiology, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA 19174); Yoshimura, M.; Muto, M.; Chi, J.; Roth, S.; Kaji, A. *Cancer Res* 37(3): 712-717; 1977.

Chondrocytes isolated from 11-day-old chicken vertebral cartilage were transformed by the wild-type Prague strain of Rous sarcoma virus (RSV) and by a temperature-sensitive mutant (ts LA 24) of Prague RSV. The morphology of the chondrocytes transformed by RSV ts LA 24 was temperature-dependent, and the change was reversible. Similar but irreversible morphological changes were observed in chondrocytes transformed by wild-type RSV. Hyaluronic acid production, deoxyglucose transport, and acetate incorporation increased markedly in the transformed chondrocytes. Compared with normal chondrocytes, most of the labeled hyaluronic acid synthesized by the transformed cells was released into the culture medium. The results support the concept of a close relationship between oncogenesis and dedifferentiation. (45 refs.)

77-6930 **A Continuous Line of Rous Sarcoma Virus-transformed Chick Embryo Cells.** (Eng) Dinowitz, M. (Dept. Microbiology, Arizona Medical Center, Univ. Arizona, Tucson, AZ 85724). *J Natl Cancer Inst* 58(2): 307-312; 1977.

A continuous line of Rous sarcoma virus (RSV)-transformed chick embryo cells was established and evaluated for RSV production and cell growth characteristics. The cells, designated RTAZ-1, are members of the only continuous line derived from chick embryos, and they have been maintained for > 3 yr and subcultured > 250 times. RTAZ-1 grow

rapidly, display uniform morphology, and release large amounts of RSV type 1. Karyotypes and DNA/DNA hybridization between RTAZ-1 DNA and normal chicken DNA were used to verify that the cells have the genomic characteristics of chicken cells. The cells have a heteroploid chromosome complement with 92-94 chromosomes predominating and a large number of microchromosomes characteristic of chicken cells. DNA from RTAZ-1 hybridized with normal chick DNA but not with human (KB) cell DNA, providing further evidence for the chicken origin of RTAZ-1. Factors that may have contributed to the establishment of RTAZ-1 are undefined, but attention is called to the culture conditions used, such as incubation temperature (39-40 C) and screening of sera for toxicity for RTAZ-1. The development of the heteroploid chromosome complement may also have contributed to the ability of these cells to grow continuously. (27 refs.)

- 77-6931 **Cell Shape and Hexose Transport in Normal and Virus-transformed Cells in Culture.** (Eng.) Bissell, M. J. (Lab. Chemical Biodynamics, Lawrence Berkeley Lab., Univ. California, Berkeley, CA 94720); Farson, D.; Tung, A. S. *J Supramol Struct* 6(1): 1-12; 1977.

Hexose transport was compared in normal embryonic fibroblast cells and cells infected with Schmidt-Ruppin Rous sarcoma virus (subgroup A) either in suspension or on monolayers. Results show that once normal and transformed cells are removed from the monolayer and placed in suspension, they transport glucose analogs at a slower rate, especially at high sugar concentrations, although the differential between normal and transformed cells is retained. Scanning electron microscopy revealed morphological differences between the two types of cells only in the flat state. Two conclusions may be drawn from the fact that the magnitude of the difference is similar to that shown by the cells on a monolayer at low sugar concentrations: (1) the difference in transport rate is not due to cell shape, topology, or state of cell cycle, (2) the high affinity hexose carrier protein does not appear to be extremely trypsin-sensitive and, therefore, may not be located in an exposed site on the membrane. (21 refs.)

- 77-6932 **The Genome-associated, Specific RNA Binding Proteins of Avian and Mammalian Type C Viruses.** (Eng) Sen, A. (Lab. Viral Carcinogenesis, NCI, Bethesda, MD 20014); Todaro, G. J. *Cell* 10(1): 91-99; 1977.

Two methods were developed for purifying specific RNA binding proteins from avian and mammalian C-type viruses. With the use of polyethylene glycol extraction in the presence of high salt concentrations and gel filtration in Sephadex 75, heterogeneous, low-mol-wt protein preparations were obtained that showed a greater extent of binding to purified

viral RNA in an in vitro assay system. Purification of radiolabeled protein from ribonucleoprotein complexes formed in vitro showed that the specific RNA binding protein component of Rous sarcoma virus was the major phosphoprotein (p19) in these viruses. Following UV irradiation of viral particles under conditions that stabilize the polyploid 70S viral RNA, the same polypeptide was directly purified from the RSV genome. Similar experiments indicated that the major phosphoproteins of mammalian C-type viruses (p12 for murine viruses and p16 for endogenous primate viruses) are also the specific RNA binding proteins and that they are also found closely associated with the 70S RNA genomes in the intact viral particles. Thus, by using two different approaches, it was shown that the major phosphoproteins of various C-type viruses are associated with the RNA genome in the virion and that they can bind specifically to the same RNA in vitro. (33 refs.)

- 77-6933 **Feline Malignant Mammary Tumors. III. Presence of C-Particles and Intracisternal A Particles and Their Relationship with Feline Leukemia Virus Antigens and RD-114 Virus Antigens.** (Eng) Calafat, J. (Div Virology, Netherlands Cancer Inst., 108 Sarphatistraat, Amsterdam, Netherlands); Weijer, K.; Daams, H. *Int J Cancer* 20(5): 759-767; 1977.

Thirty-six feline mammary tumors were examined by electron microscopy and by the indirect immunofluorescence (IFA) test with anti-feline leukemia virus (FeLV) and anti RD-114 virus sera. Intracisternal A particles (IAP) were found in 11 tumors. One of these tumors contained a few particles with electron-dense nucleoid in the cisternae of the endoplasmic reticulum. C particles were found in seven other tumors. FeLV antigens were present in 11 tumors, RD-114 virus antigen in 20. There was a good correlation between the presence of C particles and the demonstration of FeLV antigen, but none between IAP and FeLV antigens. No correlation was found between RD-114 virus antigens and any type of particle. Morphologically, the IAP in feline mammary tumors were indistinguishable from the IAP in the mammary tumors of some inbred mice. The IAP in feline mammary tumors may represent an endogenous virus, different from RD-114 virus. The role of these viruses in the etiology of feline mammary tumors is discussed. (25 refs.)

- 77-6934 **A Feline Leukaemia Virus- and Sarcoma Virus induced Tumor specific Antigen.** (Eng) Hardy, W. D. (Lab. Veterinary Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Zuckerman, E. E.; MacEwen, E. G.; Hayes, A. A.; Essex, M. *Nature* 270(5634): 249-251; 1977.

To determine whether feline oncornavirus-associated cell membrane antigen (FOCMA) is tumor-specific, cells from

both feline leukemia virus (FeLV)-infected and uninfected healthy cats and FeLV-infected and uninfected cats with naturally occurring lymphosarcoma (LSA) were studied. All FeLV-producing cell preparations from FeLV-infected LSA cats were positive for FOCMA. All LSA preparations not replicating FeLV were also FOCMA-positive. All FeLV-infected and FeLV-negative lymphocytes from cats with LSA but no circulating leukemia cells were negative for FOCMA. Sixty-three normal cell preparations, 20 FeLV-infected and 43 uninfected, from healthy cats were FOCMA-negative. Normal FeLV-infected and uninfected feline embryo lung fibroblast cultures were FOCMA-negative. Two fibrosarcoma cultures from cats with feline sarcoma virus (FeSV)-induced tumors, granulocytic tumor cells from a cat with myelogenous leukemia, and a dog fibrosarcoma culture from an FeSV-induced tumor were FOCMA-positive. Thus, FOCMA is an FeLV- or FeSV-induced tumor-specific antigen expressed on the membranes of naturally occurring feline LSA, myelogenous leukemia, and multicentric fibrosarcoma cells. (20 refs.)

77-6935 Expression of Feline Leukaemia Virus Antigens on Cat Lymphoma Cells: Kinetics of Biosynthesis. (Eng.) O'Brien, S. J. (Cell Biology Section, Lab. Viral Carcinogenesis, NCI, NIH, Bethesda, MD 20014); Boone, C. W. *J Gen Virol* 35(3): 511-523; 1977.

The kinetics of biosynthesis of feline leukemia virus-associated cell-surface antigens (FeLV-CSA) were examined in the presence of three inhibitors of cellular and/or virion gene expression: actinomycin D (transcription), cordycepin (RNA processing), and cycloheximide (translation). Cultured feline lymphoma cells (FL-74) productively infected with FeLV were examined quantitatively by a radioimmune assay for cell membrane-associated FeLV-p27 and total FeLV-CSA using a monospecific and a broadly reactive antiserum, respectively. The infected cells bound 5.6×10^5 anti-FeLV-p27 IgG molecules per cell, representing 40% of the total FeLV-CSA detected. Both p27 and the total FeLV-CSA population reappeared on the cell surface within 6-8 hr after trypsin digestion. Antigen reexpression was blocked by cycloheximide but not by actinomycin D or cordycepin. The average turnover rate of cell surface p27 and FeLV-CSA was 6-8 hr, but the messenger RNA's (mRNA's) that specify these antigens had a lifetime of at least 10 hr. Virus production was blocked in < 2 hr by cycloheximide and within 2-4 hr by actinomycin D. Virus production continued at a reduced rate for at least 6 hr in the presence of cordycepin. The difference in sensitivity to inhibitors of RNA synthesis of p27 and FeLV-CSA production (blocked in 9-10 hr) and of virus production (blocked in 2-4 hr) suggests the existence of two different RNA species that are rate limiting under the conditions of inhibition of RNA synthesis: a short-lived virion-limiting RNA and a more stable mRNA that specified p27 and the additional FeLV-CSA. (35 refs.)

77-6936 Analysis of Intracellular Feline Leukemia Virus Proteins. II. Generation of Feline Leukemia Virus Structural Proteins from Precursor Polypeptides. (Eng) Okasinski, G. F. (Dept. Microbiology and Public Health, Michigan State Univ., East Lansing, MI 48824); Velicer, L. F. *J Virol* 22(1): 74-85; 1977.

The synthesis and processing of feline leukemia virus (FeLV) polypeptides were studied in a chronically infected feline thymus cell line, F-422, which produces the Rickard strain of FeLV. Immune precipitation with antiserum to FeLV p30 and subsequent sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) were used to isolate intracellular FeLV p30 and possible precursor polypeptides. SDS-PAGE of immune precipitates from cells pulse-labeled for 2.5 min with 35 S-methionine revealed the presence of a 60,000-dalton precursor polypeptide (Pp60) as well as a 30,000-dalton polypeptide. When cells were grown in the presence of the proline analogs L-azetidine-2-carboxylic acid, a 70,000-dalton precursor polypeptide (Pp70) was found in addition to Pp60, after a 2.5-min pulse. During pulse-labeling, the cleavage of Pp60 could be partially inhibited by the general protease inhibitor phenyl methyl sulfonyl fluoride. Intracellular Pp70 and Pp60 and FeLV virions p70, p30, p15, p11, and p10 were subjected to tryptic peptide analysis. The results demonstrated that intracellular Pp70 and virion p70 were identical and that both contained the tryptic peptides of FeLV p30, p15, p11, and p10. Pp60 contained the tryptic peptides of FeLV p30, p15, and p10, but lacked the tryptic peptides of p11. Pactamycin gene ordering experiments showed that the small FeLV structural proteins are ordered as follows: p11-p15-p10-p30. The small structural proteins of FeLV are synthesized as part of a 70,000-dalton precursor. A cleavage scheme for the generation of FeLV p70, p30, p15, p11, and p10 from precursor polypeptides is proposed. (29 refs.)

77-6937 Infection of Bone Marrow Cells In Vitro with FLV: Effects on Stem Cell Proliferation, Differentiation and Leukemogenic Capacity. (Eng) Dexter, T. M. (Paterson Labs., Christie Hosp. and Holt Radium Inst., Manchester, M20 9BX, England); Scott, D.; Teich, N. M. *Cell* 12(2): 355-364; 1977.

A long-term culture system was used to analyze the replication of different biological variants of murine leukemia virus (MuLV) in bone marrow cells, the effect of MuLV on pluripotent stem cell (CFU-S) proliferation, and the effect of MuLV on CFU-S differentiation along different hematopoietic pathways. Two MuLV variants were studied in detail: the Moloney strain of lymphatic leukemia virus (M-MuLV) and the erythroleukemic Friend virus complex (FLV) consisting of the lymphoid leukemia helper virus and the defective spleen focus-forming virus (SFFV). M-MuLV and its sarcoma virus pseudotype, MSV(M-MuLV), replicated

efficiently in the bone marrow cultures; however, CFU-S were lost more readily than in uninfected ones, and the cultures soon consisted primarily of mononuclear macrophages. On the other hand, infection with FLV produced a prolonged survival of the spleen colony-forming cells, CFU-S, and CFU-C (the committed granulocytic precursor cells). Production of erythroleukemogenic SFFV continued in these cultures for > 40 wk. No erythroblastic differentiation was observed in vitro; however, neither erythroblast precursor cells nor Hb-producing cells could be detected. This suggests that the target cell for FLV is an earlier precursor cell. (33 refs.)

- 77-6938 Concanavalin A and the Production of Bovine Leukemia Virus Antigen in Short-term Lymphocyte Cultures.** (Eng) Driscoll, D. M. (Dept. Veterinary Science, Univ. Wisconsin, Madison, WI 53706); Baumgartner, L. E.; Olson, C. *J Natl Cancer Inst* 58(5): 1513-1514; 1977.

The influence of the mitogen concanavalin A (Con A) on the production of bovine leukemia virus (BLV) antigen in short-term lymphocyte cultures was determined in a single radial immunodiffusion test. Con A did not affect viral antigen production in peripheral blood lymphocytes from 60% of both experimentally and naturally infected cattle. Antigen production was stimulated by Con A in lymphocytes from 28% of the cattle, but it was inhibited in lymphocytes from 12%. Similar results were obtained with lymphocytes from both blood and lymph nodes of 10 cattle with lymphosarcoma and 10 clinically normal cattle with histologically normal lymph nodes. In sheep and goats, Con A had no effect on lymphocytes from 50%, stimulated BLV production in 43%, and inhibited BLV production in 7%. These results indicate that lymphocytes should be cultured with and without Con A to identify every BLV-infected animal. (13 refs.)

- 77-6939 Modification of Cultured Rabbit Cells by Ultraviolet-inactivated Noncytotoxic Shope Fibroma Virus.** (Eng) Crouch, N. A. (Dept. Microbiology, Univ. Iowa, Iowa City, IA 52242); Hinze, H. C. *Proc Soc Exp Biol Med* 155(4): 523-527; 1977.

The effects of UV-inactivated Shope fibroma virus (SFV) on the in vitro behavior of cloned kidney cells (DRK₁) from a New Zealand white rabbit and on the replication of vesicular stomatitis virus (VSV) were examined. DRK₁ cultures treated with SFV exposed to UV light (3.17 μ watts/cm²) for 25 sec formed multilayered cellular aggregates, most of which contained no detectable viral DNA or viral antigens. In cultures treated with nonirradiated SFV, all of the few cellular aggregates that formed synthesized viral components. Cultures infected with SFV irradiated for 100 sec to abolish infectivity resembled mock-infected cultures in appearance and lack of

viral components. The replication of VSV in DRK₁ cells was facilitated by partially inactivated SFV but inhibited by excessively irradiated SFV. The results suggest that a functional SFV genome required to alter DRK₁ cells is expressed early in the SFV replicative cycle. (8 refs.)

- 77-6940 Pseudotypes of Vesicular Stomatitis Virus with Envelope Antigens Provided by Murine Mammary Tumor Virus.** (Eng) Zavada, J. (Imperial Cancer Res. Fund Labs., Post Office Box 123, Lincoln's Inn Fields, London, WC2A 3PX, England); Dickson, C.; Weiss, R. *Virology* 82(1): 221-231; 1977.

When infected with vesicular stomatitis virus (VSV), mammary tumor cells derived from spontaneous tumors of GR and C3H mice produced at least two types of particles containing the VSV genome but expressing different envelope characteristics (VSV pseudotypes). One of these VSV pseudotypes was infectious for normal mouse mammary epithelial cells and mouse embryo cells but noninfectious for mouse 3T3 cells, mink lung cells, and Vero cells. When the mammary tumor cells were treated with dexamethasone prior to VSV infection, the titer of this pseudotype increased significantly. In contrast, the second pseudotype was infectious for mink cells but not for the other cell lines tested; the titer of this pseudotype was unaffected by dexamethasone. The first pseudotype was almost completely neutralized by murine mammary tumor virus (MuMTV) antiserum, but the second pseudotype was only partially neutralized at a higher antiserum concentration. Neither pseudotype showed the neutralization, host range, or interference properties of either ecotropic or xenotropic murine C-type viruses. These results suggest that the first pseudotype is VSV(MuMTV). The other pseudotype is less well defined but it may be a xenotropic MuMTV. A filterable agent isolated from GR mammary carcinoma cultures was able to reactivate the infectivity of VSV neutralized by antiserum. This agent, which may represent an unknown contaminating virus, was transmissible to mink cells. (38 refs.)

- 77-6941 Mouse Mammary Tumor Virus DNA in Infected Rat Cells: Characterization of Unintegrated Forms.** (Eng) Ringold, G. M. (Dept. Biochemistry, Univ. California, San Francisco, CA 94143); Yamamoto, K. R.; Shank, P. R.; Varmus, H. E. *Cell* 10(1): 19-26; 1977.

The forms of mouse mammary tumor virus (MMTV) DNA present in chronically infected rat hepatoma (HTC) cells were analyzed. Fractionation of DNA by sodium dodecyl sulfate-sodium chloride precipitation and by sedimentation through alkaline sucrose indicated that two-thirds of the viral

NA is associated with high-mol-wt cell DNA. The rest of the viral DNA is unintegrated and is present primarily as near or open circular duplexes consisting of a genome-length stand complementary to the viral RNA ('minus' strand) and 'plus' stands of subgenomic length. The unintegrated viral DNA could be found in the HTC cells from 18 days to 4 mo after infection. Approx 20% of the unintegrated MMTV DNA exists as covalently closed circular molecules (6×10^6 daltons) located principally in the nuclei of infected cells. The mode of synthesis of the unintegrated viral DNA is unknown. Since the structure of the open forms of MMTV DNA is characteristic of the product of viral RNA-dependent DNA polymerase, it is speculated that these forms might arise as a result of reverse transcription. (35 refs.)

77-6942 **Infection of Cultured Rat Hepatoma Cells by Mouse Mammary Tumor Virus.** (Eng) Ringold, P. M. (Dept. Biochemistry, Univ. California, San Francisco, CA 94143); Cardiff, R. D.; Varmus, H. E.; Yamamoto, K. R. *Cell* 10(1): 11-18; 1977.

A continuous line of buffalo rat hepatoma (HTC) cells was infected with mouse mammary tumor virus (MMTV) produced by the GR mammary tumor cell line, and the presence of viral DNA, RNA, and protein was documented in the infected cells. Uniform infection required initial exposure of the HTC cells to $> 10^5$ MMTV particles per cell. The results of chronically infected HTC cells contained 20-30 copies of MMTV DNA per diploid genome. The infected cells contained viral RNA and expressed viral antigens. Very few MMTV particles, however, were released into the medium. It had been demonstrated previously in mammary tumor cells, the intracellular concentration of viral RNA was strongly stimulated (50-150 times) by the synthetic glucocorticoid dexamethasone. It appears, therefore, that the mechanisms by which glucocorticoids regulate MMTV gene expression in mouse cells are maintained when this virus infects nonmurine cells. This study indicates that HTC cells are useful but not ideal for studying the biology of MMTV. The failure of HTC cells to support efficient replication of MMTV precludes the possibility of cloning and selecting mutants of the virus. The absence of altered growth or morphological characteristics in the infected cells prevents their use as a rapid biological assay for MMTV infection. Finally, the large number of particles required to initiate infection of HTC cells makes analysis of events early in infection impractical. (45 refs.)

77-6943 **Is There a Role for Actin in Virus Budding?** (Eng) Damsky, C. H. (Wistar Inst. Anatomy and Biology, Philadelphia, PA 19104); Sheffield, J. B.; Tusnski, G. P.; Warren, L. *J Cell Biol* 7(2, part 1): 593-605; 1977.

Electrophoretic data from both sodium dodecyl sulfate-polyacrylamide gels (SDS-PAGE) and acid-urea gels revealed a protein in purified BALB/cf C3H mouse mammary tumor virus (MuMTV) that comigrates with purified chick skeletal muscle actin. 125 I-labeling of intact and disrupted virus preparations showed that the actinlike protein was not artifactually adsorbed to the outside of the virions during isolation. Quantitative SDS-PAGE and examination of negatively stained preparations demonstrated that the actin was not due to a contaminating population of virus-free vesicles. The ultrastructure of mammary epithelial cells and of Rous sarcoma virus-transformed chick embryo fibroblasts shows that virus extrusion is associated with filament-containing cellular processes. In particular, MuMTV is released from the ends of long microvilli that contain a bundle of 6- to 8-nanometer microfilaments and share other structural features with intestinal microvilli. It is suggested that virus nucleoids require an interaction with host cell contractile proteins for their extrusion from the cell. (34 refs.)

77-6944 **Changes in Hemopoiesis During the Course of Acute LCM Virus Infection in Mice.** (Eng) Bro-Jorgensen, K. (Inst. Medical Microbiology, Univ. Copenhagen, Juliane Maries Vej 22, 2100 Copenhagen O, Denmark); Knudtzon, S. *Blood* 49(1): 47-57; 1977.

The function of hemopoietic cells in the course of acute lymphocytic choriomeningitis (LCM) virus infection was investigated in C3H/Secl mice inoculated with 10^5 mean intracranial lethal doses (LD₅₀) of the virus. During the first week of the infection, there was profound suppression of pluripotential stem cell (CFU) and in vitro colony-forming cell compartments and of 59 Fe uptake into the hemopoietic tissues. Enhanced activity of colony-stimulating factor, lack of responsiveness to erythropoietin, and appreciable titers of interferon in the blood and spleen were also noted. After the 10th day, there was a striking increase in CFU and 59 Fe uptake confined to the spleen and blood. Restoration of bone marrow, however, was delayed markedly. In late stages of infection and in persistently infected mice, no interferon activity was found. Pretreatment of mice with 850 R of x-rays before injection of LCM virus did not interfere with the amounts of interferon produced. It is suggested that interferon is the comprehensive suppressor of the hemopoietic precursor cells in the first stage of acute LCM virus infection and that these cells in the recovery period are directed into erythropoiesis. (35 refs.)

77-6945 **Selective Expression of Xenotropic Virus in Congenic HRS/J (Hairless) Mice.** (Eng) Hiai, H. (Hematology Service, New England Medical Center Hosp., Tufts Univ. Sch. Medicine, Boston, MA 02111); Morrissey, P.; Khirya, R.; Schwartz, R. S. *Nature* 270(5634): 247-249; 1977.

Differences in xenotropic virus production in HRS/J mice homozygous (hr/hr) or heterozygous (hr/+) for the hairless trait were investigated. The ecotropic virus in these mice was N-tropic, and it was readily detected in the spleen, thymus, and bone marrow of hr/hr and hr/+ mice. At no time was there a difference in virus titer between the two types of mice. Small amounts of xenotropic virus were detected in the thymuses of 2-mo-old hr/hr and hr/+ mice with little difference between the two strains. By 8 mo, however, titers in the thymuses of hr/hr mice, but not of hr/+ mice, had increased remarkably. Low titers of xenotropic virus were also detected in the spleen and bone marrow of some hr/hr and hr/+ mice. Therefore, increased expression of xenotropic virus was specifically related to age, tissue, and genotype of the mouse. This was confirmed in a mink cell assay. After several in vitro passages of xenotropic viruses in mink cells, the culture supernatant was filtered and tested for infectivity on mink and NIH-3T3 cells. None of the 48 isolates produced XC plaques on either of these lines; 46/48 isolates, however, were demonstrated to be pure xenotropic virus. Examination of ecotropic and xenotropic virus in leukemia tissues of hr/hr and hr/+ mice indicated no significant differences between preleukemic and leukemic thymus tissue for ecotropic virus, but leukemic thymic tissue had much lower xenotropic virus titers than preleukemic tissue. (8 refs.)

- 77-6946 **RNase T1-resistant Oligonucleotides of an N- and a B-tropic Murine Leukemia Virus of BALB/c: Evidence for Recombination Between These Viruses.** (Eng) Faller, D. V. (Center Cancer Res., Massachusetts Inst. Technology, Cambridge, MA 02139); Hopkins, N. *J Virol* 24(2): 609-617; 1977.

Two-dimensional gel electrophoresis was used to obtain fingerprints of ³²P-labeled RNase T1-resistant oligonucleotides derived from the SP-N (N-tropic) and LP-B (B-tropic) murine leukemia viruses of BALB/c mice. The viruses shared approx 30 of these large oligonucleotides. Furthermore, there were eight oligonucleotides unique to SP-N, six to LP-B. XLP-N viruses, apparent recombinants between these N- and B-tropic viruses, contained some but not all the specific oligonucleotides. It is possible that 3/8 SP-N-specific oligonucleotides are related to 3/6 LP-B-specific oligonucleotides, because they could arise by a single base change. They would be allelic and their inheritance in XLP-N cells would be exclusive, as is the case for 15 viruses examined to date. Three other SP-N-specific nucleotides could have arisen during tissue culture passage of SP-N. It is not known if any of the SP-N- or LP-B-specific oligonucleotides will be useful in the mapping of murine leukemia viruses. (18 refs.)

- 77-6947 **Identification of the Gross Cell Surface Antigen Associated with Murine Leukemia Virus-infected Cells.** (Eng.) Ledbetter, J. (Fred Hutchinson Cancer

Res. Center, Seattle, WA 98104); Nowinski, R. C. *J Virol* 23(2): 315-322; 1977.

The immunochemical identification of the Gross cell surface antigen (GCSA), which is produced by cells that are either exogenously infected with murine leukemia virus (MuLV) or are expressing endogenous MuLV genomes, is reported. Two methods were used to determine the relationship of GCSA to MuLV-coded proteins: (1) analysis of the GCSA typing serum (C57BL/6 anti-AKR K36) for antibodies against MuLV proteins, and (2) analysis of the GCSA typing cell (C57BL/6 E male G2) for the expression of MuLV proteins on the cell surface. The GCSA typing serum predominantly precipitated 85,000- and 95,000-dalton proteins from ¹²⁵I-labeled C57BL/6 E male G2 membrane preparations. These proteins were selectively removed from the C57BL/6 E male G2 extract by an anti-p30 immunoabsorbant. The cytotoxicity of GCSA antisera was correlated with the reaction of these sera with the 85,000- and 95,000-dalton proteins. These findings indicate that the major components of the GCSA complex are two glycosylated precursors of the viral core proteins, which contain antigenic determinants of the MuLV proteins p30, p12, and p10. Some pools of GCSA antiserum also contained antibodies against the viral envelope proteins gp70 and p15. (20 refs.)

- 77-6948 **Virus Expression in Different Tissues of Normal and Tumor-bearing Mice Inoculated with a Murine Leukemia Virus.** (Eng) Youn, J. K. (Tissue Culture and Virology Lab., E. R. No. 38, C.N.R.S., Institut Gustave-Roussy, 94800-Villejuif, France); Santillana, M.; Hue, G.; Barski, G. *Int J Cancer* 20(5): 792-797; 1977.

The evolution of virus expression in different lymphoid organs and in solid syngeneic tumors of mice inoculated with a murine leukemia virus was studied in vitro by XC coculture technique. When normal, inbred adult C57BL mice (XLII strain) were inoculated ip with 0.2 ml of a cultured Rauscher virus (RC), small amounts of virus were detected 10 days later in the bone marrow. Thereafter, no virus was found in any of the organs tested, including bone marrow, spleen, thymus, lymph nodes, and kidney. However, when age- and sex-matched parallel mice bearing syngeneic sarcomatous tumors were inoculated with the RC virus, abundant virus was detected not only in bone marrow and spleen, but also in tumors during the first 3 wk and even 6 wk post inoculation. A transient disappearance of the virus was observed around the 25th-31st days in organs and tumors of the inoculated mice. Removal of the tumor mass was followed by the rapid disappearance of virus from all the organs tested. The virus recovered from in vitro explanted and cultured tumors induced typical lymphoid leukemia in BALB/c mice inoculated as newborns. Unlike the original RC virus, this virus produced hypertrophy of the thymus and lymph nodes. (22 refs.)

7-6949 **Effect of Interferon on Production of Minimal Forms of Rauscher Leukemia Virus in Virus-producing Cell Systems.** (Rus) Soloviev, V. D. (N. F. Gama-ya Inst. Epidemiology and Microbiology, Moscow, USSR); Gatarinova, Yu. I.; Balandin, I. G.; Parfenova, T. M. *Dokl Akad Nauk SSSR* 237(1): 218-219; 1977.

To determine the mechanism of the inhibitory effect of interferon (IF) on the development of oncogenic virus-induced leukemias in mice, two leukogenic cell lines (KML-3 obtained from bone marrow of BALB/c mice with Rauscher leukemia, and KML+LB line obtained from healthy BALB/c mice and inoculated on the ninth passage with Rauscher leukemia virus) were incubated with or without IF (20 IU/ml). Virus-containing incubation fluids were then injected ip (0.5 ml) into BALB/c mice. Both KML-3 and KML+LB cells produced leukemia-inducing virus. All mice in the non-IF groups developed leukemia; av duration of survival was 30 days and 41 days, respectively, for mice injected with KML-3 and KML+LB fluids. Inoculation of BALB/c mice with KML-3 and KML+LB cells exposed to IF increased the duration of survival (66 days and 60 days, respectively); and only 14/20 mice and 16/20 mice, respectively, developed leukemia. Assessment of the content of minimal forms of oncovirus showed that exposure to IF significantly elevated production of minimal forms. These findings confirm the hypothesis that IF affects the synthesis of virion components rather than virus escape from the cell. (9 refs.)

7-6950 **Kinetic Study of Hematopoietic Stem Cells in Experimental Viral Leukemia.** (Rus) Klochko, E. V. (Inst. Chemical Physics, Acad. Sciences USSR, Moscow, USSR); Lukshin, Iu. V.; Klochko, E. V.; Krugliakova, E.; Emanuel', N. M. *Dokl Akad Nauk SSSR* 235(1): 201-204; 1977.

The kinetics of hematopoietic stem cells, possible targets of Rauscher virus, was studied in mice with Rauscher leukemia. The rate of increase in spleen wt and the induction time were studied in male BALB/c mice infected with a cell-free filtrate from the spleens of leukemic BALB/c mice 2 and 96 hr after treatment with isopropylmethane sulfonate (IPMS: 50 mg/kg ip). The induction time was 1 day in control mice (not treated with IPMS), 6 days in the group infected 2 hr after IPMS treatment, and 21 days in the group infected 96 hr after IPMS treatment. The corresponding rates of increase in spleen wt were 0.1402, 0.1642, and 0.1538 mg/day. Autoradiographic studies revealed an increased number of ³H-midine-labeled lymphocytelike cells in virus-infected animals compared with noninfected controls. The results indicate that infection with Rauscher virus produces cells with altered kinetic and functional characteristics. These cells may be actively proliferating stem cells that are capable of differentiation. (6 refs.)

7-6951 **Specific Inhibition of DNA Polymerase-associated RNase H by DNA.** (Eng) Modak, M.

J. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Marcus, S. L. *J Virol* 22(1): 243-246; 1977.

The RNase H activity associated with several RNA-directed DNA polymerases was inhibited by the addition of DNA, in contrast to the RNase H activity from enzymes devoid of polymerizing activity. Kinetic investigations of the inhibitory effect of DNA, using purified Rauscher leukemia virus DNA polymerase as the test enzyme, revealed that the addition of DNA to an ongoing RNase H activity caused an immediate cessation of the activity. However, concomitant initiation of DNA synthesis directed by inhibitory DNA occurred in the presence of appropriate substrate and primer. The data strongly support the concepts (1) that RNase H activity expressed by several mammalian oncoviral reverse transcriptases is an integral part of that molecule and (2) that the catalytic site of RNase H activity is also involved in template-primer binding. (16 refs.)

77-6952 **Rauscher-Leukemia-Virus-Related Sequences in Human DNA: Presence in Some Tissues of Some Patients with Hematopoietic Neoplasias and Absence in DNA from Other Tissues.** (Eng) Aulakh, G. S. (Div. Virology, Bureau Biologics, 8800 Rockville Pike, Building 29A, Room 2D-24, Bethesda, MD 20014); Gallo, R. C. *Proc Natl Acad Sci USA* 74(1): 353-357; 1977.

DNA from normal and neoplastic human tissues was examined for sequences related to the RNA of Rauscher murine leukemia virus (R-MuLV). A ³H-complementary DNA (³H-cDNA) probe synthesized from the RNA genome of R-MuLV and purified by hybridization to R-MuLV 70S RNA was hybridized to DNA from human tissues. Sequences complementary to R-MuLV cDNA were found in the DNA from tissues of 2/8 leukemia patients, 3/10 Hodgkin's disease patients, and 1 patient with multiple myeloma. DNA from the spleen and kidney of a patient with aortic insufficiency, from the uninvolved lung of a patient with Burkitt's lymphoma, and from uninvolved tissues of leukemia patients did not contain detectable R-MuLV-related sequences. Differences in thermal elution profiles indicate that the virus-related sequences in the DNA from the neoplastic tissues were related but not identical to R-MuLV sequences. These nucleotide sequences are not the same as the proviral sequences of baboon C-type virus previously found in other leukemia patients, because there is no sequence homology between nucleic acids from R-MuLV and baboon virus. The absence of these nucleic acid sequences from many tissues of patients with neoplastic and nonneoplastic diseases suggests that they are not endogenous but are acquired after fertilization. Taken together, the results show at least two independent sets of oncornavirus-related sequences in the DNA from some leukemia patients. Although the mode, source, time of acquisition and the relevance to etiology are speculative, interspecies transmission of one or both agents may be involved. (41 refs.)

- 77-6953 **Complexing Rauscher Leukemia Virus Reverse Transcriptase with Human Plasma Ribonuclease from Hodgkin's Disease Patients.** (Eng) Bandyopadhyay, A. K. (Section Immunology and Cell Biology, Lab. Molecular Biology, NCI, HIN, Baltimore Cancer Res. Center, Baltimore, MD 21211); Levy, C. C.; Mardiney, M. R. *J Biol Chem* 252(21): 7783-7787; 1977.

Human ribonucleases were purified from the sera of four Hodgkin's disease patients by sequential column chromatography. The purified enzyme interacted with the reverse transcriptase of Rauscher leukemia virus and formed an additive complex with a mol wt of 130,000. RNase and oligo(dG)-directed reverse transcriptase activities were diminished in the complex. The complex could be dissociated with the subsequent restoration of both activities in the presence of spermidine. The mol wt of the complex suggests that the two RNase molecules bind to a single reverse transcriptase molecule. (26 refs.)

- 77-6954 **Purification and Properties of Rauscher Leukemia Virus DNA Polymerase and Selective Inhibition of Mammalian Viral Reverse Transcriptase by Inorganic Phosphate.** (Eng) Modak, M. J. (Memorial Sloan-Kettering Cancer Center, New York, NY 10021); Marcus, S. L. *J Biol Chem* 252(1): 11-19; 1977.

Rauscher leukemia virus RNA-directed DNA polymerase was purified > 90% by affinity chromatography on polycytidylate-agarose, with > 85% recovery of input enzymatic activity. The purified enzyme has a mol wt of approx 70,000 and appears to consist of a single polypeptide chain. The enzyme is free of DNase but has RNase H activity. Analysis of the requirements for optimal rates of DNA synthesis by this enzyme using synthetic and natural template-primers revealed template-specific variations in these requirements. DNA synthesis catalyzed by Rauscher leukemia virus DNA polymerase was inhibited by the addition of inorganic phosphate. An analysis of the mechanism of phosphate inhibition, carried out with the synthetic template-primer poly(A)-(dT)₁₀, suggested that it may involve the substrate binding site of the enzyme and that phosphate ions affect the process of chain elongation more than that of initiation. The extension of these studies to DNA synthesis catalyzed by a variety of mammalian C-type viral reverse transcriptases revealed that low levels (≤ 2 mM) of inorganic phosphate strongly inhibited DNA synthesis. The susceptibility to phosphate inhibition appears unique to mammalian C-type viral enzymes, since the B-type viral enzyme, *Escherichia coli* DNA polymerase I, avian myeloblastosis virus and Mason-Pfizer monkey tumor virus reverse transcriptase, and cellular DNA polymerases α and γ were not inhibited by inorganic phosphate. The phosphate inhibition of various DNA polymerases, therefore, provides a new basis for the differentiation of the sources and nature of these enzymes. (28 refs.)

- 77-6955 **Effects of Streptovaricins and Their Degradation Products on Infectivity of Rauscher Leukemia Virus.** (Eng) Li, L. H. (Research Lab., Upjohn Co., Kalamazoo, MI 49001); Clark, T. D.; Cowie, C. H.; Swenberg, J. A.; Renis, H. E.; Rinehart, K. L. *J Natl Cancer Inst* 58(2): 245-249; 1977.

The virocidal effects of streptovaricin A (SvA), SvC, SvD, streptoval (Sval) C, Sval Fc, and streptovarone were measured by incubating the drugs with Rauscher leukemia virus (RLV) for 60 min at 37 C prior to dilution and addition to BALB/3T3 cells or prior to ip injection into BALB/c mice. Inhibition of virus infectivity was determined by the simultaneous administration of drug and virus to the cells or the animals. The in vitro and in vivo assays for drug effects were plaque formation and splenomegaly, respectively. The Sv degradation products (Sval C, Sval Fc, and streptovarone) were most inhibitory in the in vitro assay, followed by SvD; SvA and SvC were least active. At 0.0625 micromole (μ mol), the three Sv degradation products inactivated > 90% of the RLV. In the in vivo assay, at 0.06 μ mol, streptovarone, Sval C, and SvD showed 78%, 62%, and 29% inhibition of splenomegaly, respectively; SvA and SvC were inactive. There was a direct relationship between inhibition of RNA-directed DNA polymerase by these drugs and their virocidal effects. No drug given at the time of infection, however, showed any significant effect on virus infective processes in vivo or in vitro. The lack of therapeutic effect of the drugs could be partially due to their unfavorable physiologic and pharmacologic characteristics. (19 refs.)

- 77-6956 **Viral Reverse Transcriptase Suppression Associated with Erythroid Differentiation of Friend Leukemia Cells.** (Eng) Ebert, P. S. (Viral Biology Branch, NCI, NIH, Public Health Service, U.S. Dept. Health, Education, and Welfare, Bethesda, MD 20014); Buell, D. N. *J Natl Cancer Inst* 58(3): 635-640; 1977.

Friend erythroleukemia T3-C12 cells, which produce Friend murine leukemia virus (F-MuLV) and can be induced to synthesize Hb by dimethyl sulfoxide (DMSO), were monitored for viral RNA-dependent DNA polymerase reverse transcriptase (RT) activity. The amount of viral 60S-70S RNA released from DMSO-treated cells was unaffected or was increased compared with that from control cells, but RT activity from treated cells was decreased. Accordingly, the specific activity in F-MuLV from DMSO-treated cells, expressed as RT/70S RNA, decreased to 8% of the control activity. 5-Bromo-2-deoxyuridine reversed the DMSO-induced differentiation process and the suppression of RT activity. Cell-free F-MuLV incubated with and without DMSO showed the same RT activity, indicating that DMSO itself did not inhibit RT activity. However, when F-MuLV containing pellets from control and DMSO-treated culture fluids were mixed, there was marked inhibition of the control RT activity, suggesting that RNase hybrid activity was stimulated or that an

inhibitor was produced. Assays of F-MuLV-RNase hybrid showed that the activity of the RT was decreased from control and DMSO-treated cells showed no difference in activity, which indicated that a specific RT inhibitor was produced or activated. The additions of certain nucleotide triphosphates to RT incubation mixtures did not stimulate RT activity in DMSO-treated F-MuLV, suggesting that phosphatase was not responsible for the inhibition. The results suggest that DMSO reduced viral RT activity in T3-2 cells by stimulating the production of an inhibitor, the nature of which is unknown. (25 refs.)

6957 Immunofluorescent Analysis of Expression of the RNA Tumor Virus Major Glycoprotein, gp71, on Surfaces of Virus-producing Murine and Other Mammalian Species Cell Lines. (Eng) Cloyd, M. W. (Dept. Pathology, Duke Univ. Medical Center, Durham, NC 27710); Bolognesi, D. P.; Bigner, D. D. *Cancer Res* 37(3): 930; 1977.

The specificity of a rabbit antiserum against the purified major glycoprotein, gp71, of Friend murine leukemia virus was determined for several virus-producing mouse, feline, and non-ape cell lines by viable cell membrane immunofluorescence absorption. Among the murine cells examined, Friend 1 type specificity was shared only with Rauscher virus-producing cells, and a group specificity was present for all murine leukemia virus-producing cells tested. Friend and Rauscher murine leukemia virus-infected cells shared interspecies cross-reactivity with feline leukemia and gibbon lymphoma virus-producing cells. Moloney, Gross, and Rauscher virus-producing murine cells shared some but not all of these gp71 interspecies determinants with the feline and gibbon cells. Immunoferritin electron microscopy localized the gp71 antigenic determinants on both virus and cell membranes. (40 refs.)

6958 Immunofluorescent Analysis of Expression of the RNA Tumor Virus Major Glycoprotein, gp71, on the Surfaces of Normal Murine Cells. (Eng) Cloyd, M. W. (Dept. Pathology, Duke Univ. Medical Center, Durham, NC 27710); Bolognesi, D. P.; Bigner, D. D. *Cancer Res* 37(3): 931-938; 1977.

The expression of the major glycoprotein, gp71, of murine leukemia virus on the surface of a variety of normal murine cells was studied with a monospecific rabbit anti-serum against purified Friend murine leukemia virus gp71. In a viable cell membrane immunofluorescence assay, most established and early passage normal murine cell lines were significantly reactive with the antiserum, irrespective of neoplastic transformation, strain genotype, or whether they were of embryonic or adult tissue origin. The only cells that did not express detectable gp71 determinants were the BALB/3T3 cells. Although some Friend gp71 interspecies reactivity was

discernible on normal murine cells, the principal reactivity was group-specific. Fresh thymocytes from BALB/cJ (G_h-), C57BL/6J(G_h-) and 129/J (G_h) mice were also reactive with the Friend gp71 antiserum; this activity, as well as that of an antiserum prepared against purified AKR gp71, was also group-specific. No activity discriminating G_h- from G_h+ thymocytes was observed with the Friend or AKR antisera. (33 refs.)

77-6959 Friend Strain of Spleen Focus-forming Virus Is a Recombinant Between Ecotropic Murine Type C Virus and the env Gene Region of Xenotropic Type C Virus. (Eng) Troxler, D. H. (Lab. Tumor Virus Genetics, NCI, Bethesda, MD 20014); Lowy, D.; Howk, R.; Young, H.; Scolnick, E. M. *Proc Natl Acad Sci USA* 74(10): 4671-4675; 1977.

Spleen focus-forming virus (SFFV), a replication-defective murine leukemia virus (MuLV) that causes the rapid transformation of certain hematopoietic target cells, has acquired specific xenotropic viral genetic information not contained in Friend helper virus. Molecular hybridization experiments with a complementary DNA (cDNA-SFFV) that detects xenotropic sequences in SFFV indicated that the sequences were derived from the env gene region of murine xenotropic virus. cDNA-SFFV hybridized to viral RNA from certain recombinant viruses that demonstrate replicative properties associated with the envelope glycoprotein of xenotropic virus. In addition, mapping data on the genome of a recombinant replicating MuLV were consistent with the location of the xenotropic sequences in the env gene region. The significance of the acquisition of these xenotropic viral sequences by SFFV is discussed with regard to their possible role in the rapid leukemogenicity of SFFV, and an analogy is drawn between the formation of SFFV and the formation of Kirsten and Harvey sarcoma viruses. (23 refs.)

77-6960 Model Studies on Virus-induced Tumors and Their Immunological Treatment. (Ger) Schafer, W. (Max-Planck-Institut für Virusforschung, Spemannstrasse 35/III, D-7400 Tübingen, W. Germany). *Klin Wochenschr* 55(17): 835-846; 1977.

A study of the serological properties of murine leukemia virus indicated that the viral surface glycoprotein gp71 had a major role in immunological defense mechanisms demonstrated in mice by gp71 vaccination. The induced immunity was specific and not operative against endogenous murine C-type viruses belonging to other serotypes. Antibodies to this glycoprotein were therapeutically effective against murine leukemia virus infections in mice and feline leukemia virus infections in cats. (36 refs.)

- 77-6961 **Isolation and Comparison of Murine Leukemia Virus-related Glycoproteins from AKR and New Zealand Mice.** (Eng) Kennel, S. J. (Cancer and Toxicology Program, Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830). *J Virol* 22(1): 168-174; 1977.

The major glycoprotein (gp70) of murine leukemia virus occurs free of virus in the serum and body fluids of certain strains of mice. These glycoproteins were isolated from New Zealand Black (NZB) mouse ascites fluid and from AKR and New Zealand White (NZW) mouse serum by immunoaffinity chromatography and compared by immunological tests and peptide mapping. Glycoproteins gp70-NZB and gp70-NZW were indistinguishable by all criteria tested, and they were more closely related to the gp70 from Moloney leukemia virus than was gp70-AKR. (28 refs.)

- 77-6962 **Transient Virus Expression During Murine Leukemia Induction by X-Irradiation.** (Eng) Haas, M. (Dept. Cell Biology, Weizmann Inst. Science, Rehovot 76 100, Israel). *J Natl Cancer Inst* 58(2): 251-257; 1977.

Virus expression during leukemia induction by x-irradiation was investigated in 5-wk-old female mice receiving four whole-body x-irradiations at weekly intervals. A peak of murine leukemia virus (MuLV) group-specific antigen (gsa)-positive cells occurred in the bone marrow starting on day 8 after irradiation, and it lasted for 3 wk. About 1 wk after virus replication was detected in the bone marrow cells, MuLV gsa-positive cells were detected in the thymus and they lasted for 2 wk. MuLV gsa-positive cells disappeared from the bone marrow and thymus cells and were not seen again for the life of the animals whether or not the mice contracted overt leukemia. During the period when MuLV gsa-positive bone marrow cells were found, XC-positive syncytia-producing bone marrow cells were also seen. Virus information was expressed, therefore, for a limited duration, long before any signs of leukemia were evident. MuLV gsa-positive thymocytes taken from mice 4 wk after x-irradiation were cocultivated with a series of indicator cells. B-tropic virus, in addition to a xenotropic virus, was isolated from these cells. Ecotropic virus was not found in normal mouse thymocytes, in irradiated thymocytes a few days after termination of x-irradiation, or in most primary thymomas. All thymocytes produced only xenotropic virus in the cocultivation assays. Expression of the ecotropic virus was, therefore, transient. These findings indicate that the etiologic agent of radiation-induced leukemia acts transiently and is first induced in an organ not clearly involved in the ultimate overt disease. It is suggested that a similar situation may exist in some types of human cancer in which viruses have not been found. (37 refs.)

- 77-6963 **A Discrepancy in XC and Oncogenicity Assays for Murine Leukemia Virus in AKR Mice.**

(Eng) Hays, E. F. (Lab. Nuclear Medicine and Radiation Biology, Sch. Medicine, Univ. California, Los Angeles, CA 90024); Vredevoe, D. L. *Cancer Res* 37(3): 726-730; 1977.

Normal tissues and lymphomas of AKR mice were studied for in vitro murine leukemia virus activity, determined by the XC plaque assay, and for their ability to accelerate lymphoma development after inoculation into newborn animals. Normal tissues from healthy mice up to 7 mo of age had XC activity but no oncogenic activity. The XC activity persisted and weak oncogenic activity appeared in older mice. Cocultivation of normal young cells with NIH Swiss mouse embryo cells did not result in oncogenic activity, although XC virus titers increased. Host range studies of a cell-free filtrate of a virus-accelerated lymphoma showed that the virus, as measured by RNA dependent DNA polymerase and group-specific antigen, replicated in NIH Swiss mouse embryo and wild mouse embryo cells, but not in human rhabdomyosarcoma, normal rat kidney, rabbit cornea, or BALB/c embryo cells. Virus, as measured by the XC plaque assay, grew better in NIH than in BALB/c embryo cells. Both of these lines propagated virus, as measured by the oncogenicity assay. Supernatants of an in vitro cell line from a virus-accelerated lymphoma did not produce XC plaques but they were oncogenic. Those from two lines of spontaneous lymphomas were negative in both assays, although one of the supernatants became XC-positive after propagation in NIH Swiss mouse embryo cells. The question of whether the oncogenic activity that emerges with age in AKR is due to the expression of a new virus or a variant of the persistent XC virus is discussed. (18 refs.)

- 77-6964 **Viral Proteins Expressed on the Surface of Murine Leukemia Cells.** (Eng) Ledbetter, J. (Fred Hutchinson Cancer Res. Center, Seattle, WA 98104); Nowinski, R. C.; Emery, S. *J Virol* 22(1): 65-73; 1977.

Immune precipitation techniques in conjunction with ¹²⁵I-lactoperoxidase surface labeling showed that the membranes of AKR mouse leukemia cells contain the murine leukemia virus envelope protein gp70 and the precursor polyprotein of the viral internal (core) structural proteins. Both gp70 and the core polyprotein are represented on the cell surface as glycoproteins, as evidenced by incorporation of ³H-glucosamine into their structure and the binding of these proteins to lectins. The glycosylated core polyprotein exists in at least two serologically distinguishable forms: the 95,000-dalton polyprotein reacts with antisera against viral proteins p30, p12, and p10, but the 85,000-dalton polyprotein reacts only with antisera against p30 and p12. Additional heterogeneity in these cell-surface polyproteins was observed with leukemias induced by exogenous leukemia viruses. Spontaneous leukemia cells of AKR mice invariably expressed gp70 and the core polyprotein on their cell surface; normal thymocytes of young AKR mice expressed gp70, but not the core polyprotein, on their surface. (26 refs.)

6965 **Biochemical Evidence That MCF Murine Leukemia Viruses Are Envelope (*env*) Gene Recombinants.** (Eng) Elder, J. H. (Scripps Clinic and Res. Foundation, Dept. Cellular and Developmental Immunology, La Jolla, CA 92037); Gautsch, J. W.; Jensen, F. C.; Lerner, R.; Hartley, J. W.; Rowe, W. P. *Proc Natl Acad Sci USA* (10): 4676-4680; 1977.

A novel class of murine C-type virus (MCF), some strains of which are highly oncogenic in the AKR acceleration test, has recently been isolated from the premalignant and malignant lymphomas of AKR mice. The biology of these viruses suggests that MCFs are the product of recombination between endogenous ecotropic and xenotropic viruses and, further, that the recombination has taken place within the envelope (*env*) gene that encodes the surface glycoprotein (gp70) of the virion. The gp70's of four MCF isolates were compared with the gp70's of various possible parental viruses by tryptic peptide analysis. In addition, the tryptic peptides of the *gag* gene products p30 and p15 from several of these viruses were compared. The results led to the following conclusions: (1) the gp70's of the MCF viruses are not identical to one another and are different from the gp70's of the possible parental viruses tested; (2) the MCF virus gp70's have tryptic peptides in common with xenotropic virus gp70's, as well as with ecotropic virus gp70's; and (3) the *gag* region protein, p30, of the MCFs tested is identical to the p30 of xenotropic viruses, suggesting that the 5' end of the recombinant viruses is of *Akv* origin. The findings are discussed with respect to the possibility of a recombinant virus in leukemogenesis in AKR mice. (16 refs.)

6966 **Demonstration of Different Glycosylated Antigens in C-type Virus-transformed and Infected Cells by Antiserum to Murine Leukemia Virus.** (Eng) Robey, M. (Center Microbiology and Cell Biology, Instituto Venezolano de Investigaciones Cientificas, Apartado 1827, Caracas, Venezuela); Bacalao, J.; Rieber, M.; Alonso, G. *Cancer Res* 37(4): 1165-1169; 1977.

Surface glycoprotein expression was studied in normal rat embryo and kidney cells, C-type virus-transformed cells, and virus-infected cells. Polyacrylamide gel electrophoresis and autoradiography of ³H-glucosamine-labeled cells revealed eight bands of similar electrophoretic mobility in all cells. The chromolecular radioactivity decreased in pronase-treated cells. When reacted with goat antiserum to disrupted Moloney murine leukemia virus, most transformed cells exhibited two glycoprotein components with an approx mol wt of 69,000 daltons. In contrast, C-type virus-infected cells exhibited radioactivity mainly in a region nearer to that of the major 69,000-dalton viral glycoprotein. No comparable components were detected from the reaction of transformed or infected cells with preimmune serum (control serum which showed no reactivity with the virus) or from the reaction of normal cells with immune serum. (16 refs.)

77-6967 **Genetic Studies of the Ploidy of Moloney Murine Leukemia Virus.** (Eng) McCarter, J. A. (Cancer Res. Lab., Univ. Western Ontario, N6A 5C1, London, Ontario, Canada). *J Virol* 22(1): 9-15; 1977.

An assay for Moloney murine leukemia virus (M-MLV) is described that makes use of the morphologically altered foci in nonproducer mouse cells (15F) carrying murine sarcoma virus. The ratio of titers obtained for wild-type (*wt*) M-MLV at 39 and 34 C was 1.05, but the ratio for a temperature-sensitive mutant (*ts3*) defective in a late viral function was 0. A murine cell line (TB) infected with both viruses produced *wt*, *ts*, and particles of mixed parentage at 34 C; the heterozygotes (*hz*) had 39/34 C titer ratios of 0.06-0.84. To eliminate possible interference by multiploid particles with determination of the proportions of the three types of particles, the virus produced by the mixed infected cells at 34 C was distributed by velocity sedimentation in a sucrose gradient, and virus was picked from the lightest part of the gradient. The proportions of *ts*, *wt*, and *hz* were 0.27, 0.47, and 0.47. Those particles identified as *hz* segregated *ts*, *wt*, and *hz* in the proportions 0.24, 0.27, and 0.49, respectively. These values were not significantly different from those predicted from a diploid model of the genome. (23 refs.)

77-6968 **Cleavage Map of Linear Mouse Sarcoma Virus DNA.** (Eng) Canaani, E. (Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD 20014); Duesberg, P.; Dina, D. *Proc Natl Acad Sci USA* 74(1): 29-33; 1977.

Proviral DNA transcribed from Moloney murine sarcoma virus RNA was isolated from newly infected NIH/3T3 mouse cells. Three forms of viral DNA were observed: (1) a linear double-stranded form of 3.4×10^6 daltons that constituted the major species and was thought to be a complete transcriptase (monomer) of viral RNA; (2) a fast-sedimenting form bigger than the monomeric unit, which could be either integrated provirus or concatamers; and (3) covalently closed circles of monomer size representing 5% or less of the total viral DNA in the cell. The linear DNA was cleaved into two fragments by the restriction endonucleases *Hind*III and *Hae*II and into three fragments by *Hinc*II. The fragments of the viral DNA added up to approx 3.4×10^6 daltons; this and the uniform size of the linear DNA indicated that the viral DNA has unique ends and a complexity of 3.4×10^6 daltons. The different cleavage fragments were ordered with respect to each other and the 3' end of the viral RNA. Fragments from both ends of the linear DNA hybridized to sequence(s) at the 3' end of the viral RNA, suggesting that a short redundant sequence exists at both termini of the genome. (30 refs.)

77-6969 **Cells Transformed by Certain Strains of Moloney Sarcoma Virus Contain Murine p60.** (Eng) Robey, W. G. (Lab. DNA Tumor Viruses, NCI, Bethesda, MD 20014); Oskarsson, M. K.; Vande Woude, G. F.;

Naso, R. B.; Arlinghaus, R. B.; Haapala, D. K.; Fischinger, P. J. *Cell* 10(1): 79-89; 1977.

A 60,000-dalton polypeptide (p60) containing murine p30 was detected in cells of five mammalian species (dog, cat, mouse, human, and rat) transformed by the m1 isolate of murine sarcoma virus (m1MSV) by using antiserum prepared against purified virion p60. Little or no murine p30 was detected in the m1MSV-transformed cells, suggesting that the previously reported murine group p30 antigenic reactivity of MSV-transformed, sarcoma-positive, leukemia-negative (S+L-) cells is due to p60. Pulse-chase studies in cells producing the feline leukemia virus pseudotype of Moloney sarcoma virus [m1MSV(FeLV)] showed that p60 is the largest polypeptide detectable during the pulse and that intracellular p60 is not cleaved into smaller polypeptides during chase periods of up to 10 hr. The lack of p60 cleavage in virions during cell-free incubation suggests that when p30 is produced, it is rapidly packaged into virions. Since p30 was not detected in the S+L- cells, cleavage to p30 may require virus assembly. Both p60 and p70 were detected in cells transformed by the m3 isolate of MSV (m3MSV), but no immunoprecipitable polypeptides were detected in HT-1 cells (derived from a hamster tumor induced by MSV). The accumulation of murine p60 in m1MSV-transformed cells indicates that p60 is specified by this genome. Although sarcoma sequences may be required for the maintenance of transformation, the defective processing of the gene product of common leukemia sequences detected in all mammalian sarcoma virus genomes may contribute to the transformation event. Even if p60 is not related to transformation, its stability in cells may reflect how virus transformation antigens are metabolized. (40 refs.)

77-6970 The Effect of Cyclophosphamide on MSV-H Oncogenesis. (Eng) Branca, M. (Dept. Microbiology, Istituto Superiore di Sanita, Rome, Italy); Nicoletti, L. *Br J Cancer* 36(4): 487-492; 1977.

The effect of cyclophosphamide (CP) was investigated in 8- to 9-day-old BALB/c mice who received the drug either 24 hr before (A) or 24 hr after (B) sc injection of murine sarcoma virus (Harvey). Three tumors occurred in 11 Group A mice, two in 15 Group B mice, at the 50- and 100-mg/kg doses of CP only. No tumors resulted with 150 mg/kg. However, 4/5 control mice infected with virus only had tumors. Compared with controls, CP-treated mice also had an earlier incidence of tumors. Various mechanisms for the protective effect of CP are discussed. (16 refs.)

77-6971 Glycopeptides from Epithelial Cell Mutants: Temperature Sensitive for the Transformation

Phenotype. (Eng) Pietropaolo, C. (Istituto di Chimica Biologica, Facolta di Medicina e Chirurgia Universita di Napoli, Via Sergio Pansini 5, Naples, Italy 80131); Yamaguchi, N.; Weinstein, I. B.; Glick, M. C. *Int J Cancer* 20(5): 738-747; 1977.

Fucose-labeled surface glycopeptides from normal and transformed epithelial cells were compared by cochromatography on Sephadex G-50. The material from rat epithelial cells transformed in vitro or from hepatoma cells in culture elute earlier than the fucose-containing glycopeptides from normal rat epithelial cells. A transformed epithelial cell mutant that is temperature-sensitive for maintenance of the transformed phenotype varied in its Sephadex G-50 profile of cell-surface glycopeptides when grown at the permissive (36 C) or nonpermissive (40 C) temperature. When grown and labeled at 36 C, the gel filtration profile of the glycopeptides resembled that of transformed cells. At 40 C, there was an enrichment of later-eluting glycopeptides. These differences were more striking in confluent-phase cultures than in log-phase cultures. They were reversible following upward or downward shifts in growth temperature, although there was a lag of at least 6 hr before the alteration could be demonstrated. (21 refs.)

77-6972 Continued Presence of Similar Transformation-associated Antigens Related to Murine Oncor-navirus Proteins in Transformed Cells, Morphological Revertants, and Cells Restricted in the Expression of Transformation. (Eng) Rieber, M. (Center Microbiology and Cell Biology, Instituto Venezolano de Investigaciones Cientificas, Apartado 1827, Caracas, Venezuela); Bacalao, J.; Rieber, M. *Cancer Res* 37(4): 1170-1174; 1977.

The alteration of transformation-related antigens was investigated in rat NT₃-KR cells transformed by a temperature-sensitive derivative of B77 virus. These cells revert to a normal phenotype at the nonpermissive temperature (37 C) but continue to retain the viral genome. In the presence of dibutyl cyclic AMP, normal goat serum detected some differences in glycoprotein expression in cells grown at the permissive (33 C) and nonpermissive temperatures. However, a specific goat antiserum to murine leukemia virus revealed the presence of a major 100,000-dalton species in cells grown at either temperature. Similar experiments were carried out on non-producer BALB/c mouse cells transformed by Kirsten murine sarcoma virus and their corresponding flat revertants, which exhibit normal growth properties. When reacted with the specific antiserum, both cell types exhibited a major 120,000-dalton component. The glycoprotein components detected by the immune serum may represent a cellular macromolecule antigenically related to an interspecies C-type viral species the concentration of which increases in transformed cells. (10 refs.)

7-6973 **Heparan Sulfates of Mouse Cells. Analysis of Parent and Transformed 3T3 Cell Lines.** (Eng) Underhill, C. B. (Dept. Pediatrics, Univ. Chicago, Chicago, IL); Keller, J. M. *J Cell Physiol* 90(1): 53-59; 1977.

Because a transformation-dependent change in the surface heparan sulfate of subconfluent 3T3 cells has been reported a correlation with the loss of contact inhibition of growth, heparan sulfate from the surface of normal and transformed mouse cells at different cell densities was examined by ion-exchange chromatography. The heparan sulfate from new isolates of Swiss 3T3 cells transformed by simian virus 40 eluted from DEAE-cellulose at a lower ionic strength than that from the parent cell type. For both parent and transformed 3T3 cells, the heparan sulfates from low and high density cultures were the same. The heparan sulfate from Balb/c 3T3 cells transformed with Kirsten murine sarcoma virus eluted from DEAE-cellulose prior to that from parent Balb/c 3T3 cells. These results extend the transformation-dependent change in heparan sulfate to the Balb/c 3T3 cell line and to cells transformed with an RNA virus. It is concluded that the heparan sulfate of mouse 3T3 cells undergoes a structural alteration as a result of transformation, that this alteration is not caused by extended passage in culture, and that it is dependent of cell density. (10 refs.)

7-6974 **Differential Genetic Susceptibility of Cultured Human Skin Fibroblasts to Transformation by Kirsten Murine Sarcoma Virus.** (Eng) Pfeffer, L. M. Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021; Kopelovich, L. *Cell* 10(2): 313-320; 1977.

An investigation was made of the susceptibility of human skin fibroblast cultures from subepidermoid biopsies of (1) individuals with adenomatosis of the colon and rectum (ACR), (2) their F₁ ACR progeny and spouses, and (3) healthy volunteers to transformation by Kirsten murine sarcoma virus (Ki-MSV). On day 2 of culture, the cells were treated with DEAE-dextran (mol wt 2×10^6 daltons) and infected with 10-fold serial dilutions of virus. Cell cultures from all ACR individuals and several of their asymptomatic F₁ ACR progeny were 100 to 1000 times more susceptible to transformation than the normal skin fibroblast cultures. The F₁ ACR cell cultures that were not contact-inhibited and grew in low serum were susceptible, but those that were contact-inhibited and did not grow in low serum were resistant to Ki-MSV transformation. The 2×10^6 -dalton DEAE-dextran was 20 to 100 times more efficient for transformation than the one of 2×10^5 daltons. Transformed fibroblasts were positive for murine leukemia group-specific antigen and reverse transcriptase. Transformed cultures grew with greater efficiency on methocel than cultures from normal persons; the former also produced tumors when injected into BALB/c nu/nu

mice. The differences in susceptibility to transformation are probably due to differences in the transformation process itself rather than to an early stage defect or to a defect in virus replication. (24 refs.)

77-6975 **C-Type Virus from Cells of the Spontaneous Lymphosarcoma of CC57Br Mice: Characteristics of Virion Polymerase Activity.** (Rus) Tatosyan, A. G. (Inst. Experimental Biology, Acad. Sciences Armenian SSR, Erevan, USSR); Lovenetsky, A. N.; Arsenyan, S. G.; Kiselev, F. L. *Vopr Virusol* (3): 348-354; 1977.

The results of a detailed analysis of the C-type virus (virus OP) isolated from spontaneous lymphosarcomas of CC57Br mice are presented. A characteristic feature of OP virus RNA-dependent DNase (reverse transcriptase) was the termination of polymerase reaction. This phenomenon was not solely due to the presence of an inhibitor, and it was suggested that it was associated with a still unknown deficiency of the enzyme system. Sedimentation analysis of OP virus reverse transcriptase showed the existence of two molecular forms (4.8S and 6.5S, respectively). It is not known whether the observed structural complexity of the enzyme (provided that it is not an artifact) has anything to do with the termination phenomenon. (14 refs.)

77-6976 **Infectious Murine Type-C Viruses Released from Human Cancer Cells Transplanted into Nude Mice.** (Eng) Suzuki, T. (Dept. Pathology, Niigata Univ. Sch. Medicine, 1-Bancho, Asahimachi-dori, Niigata 951, Japan); Yanagihara, K.; Yoshida, K.; Seido, T.; Kuga, N.; Shimamoto, Y.; Oboshi, S. *Gann* 68(1): 99-106; 1977.

Electron microscopy of cells from nine human tumors (choriocarcinoma, acute lymphocytic leukemia, 2 lung cancers, 2 neuroblastomas, 2 liposarcomas, and a cancer of unknown origin) heterotransplanted into nude mice revealed C-type virus particles in both lung cancers, both neuroblastomas, the cancer of unknown origin and one liposarcoma. The virus particles were also found in cultures derived from the virus-positive tumors. They occurred mostly extracellularly, but a few particles were also encountered in the budding process. Tumor homogenates of cells that produced virus and high complementation fixation test titers for murine group-specific antigen were correlated closely with statistical virus counts. The values obtained were unchanged after culture in nude mice. The viruses were confirmed to be of nude mouse origin. Since the murine C-type virus propagated in human cancer cells can readily infect other virus-free permissive human cells in vitro, care should be taken in handling these cultures. (18 refs.)

- 77-6977 **Virus-specific Transcription in 3T3 Cells Transformed by the *ts-a* Mutant of Polyoma Virus.** (Eng) Bachelier, L. T. (Tumor Virology Lab., Salk Inst., San Diego, CA 92112). *J Virol* 22(1): 54-64; 1977.

Virus-specific RNA transcription in 3T3 cells transformed by the temperature-sensitive *a* (*ts-a*) mutant of polyoma virus was measured by RNA-excess hybridization to the separated strands of polyoma DNA. In two cloned sublines maintained at 39 C, the nonpermissive temperature for the *A* gene function, RNA transcripts of a large fraction of the early (E) strand were detected in both nuclear and cytoplasmic RNA fractions, but no late (L) strand transcription was detected. A shift to 31.5 C, the permissive temperature, induced viral DNA replication and virus production accompanied by L-strand transcription. In two independently derived noninducible cell lines, L-strand transcription was never observed, even after cultivation at the permissive temperature. A smaller fraction of the E strand was transcribed in each noninducible cell than in its inducible parent, and this difference was further characterized as a lack of transcripts of portions of *Hpa*II restriction endonuclease fragments 2 and 6. (21 refs.)

- 77-6978 **Polyoma Virus Transcription In Vitro.** (Eng) Condit, R. C. (Dept. Molecular Virology, Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Cowie, A.; Kamen, R.; Birg, F. *J Mol Biol* 115(2): 215-235; 1977.

Polyoma virus transcription was studied in vitro using mouse 3T3 cells infected with the A2 strain of polyoma virus. Preliminary studies indicated that the max time for harvest was 30 hr after infection. Electrophoresis on agarose gels revealed that most of the viral DNA was located in fraction III. There were approx equal amounts of supercoiled and open circular viral DNA in this fraction. However, only a small amount was active in transcription, and the sedimentation value for the active complex was 23S. Under standard incubation conditions, ribonucleoside triphosphate incorporation into acid-insoluble material by fraction III was linear for at least 60 min, but it could continue for up to 24 hr. Incorporation was inhibited by low concentrations of α -amanitin, which specifically inhibit RNA polymerase II. If actinomycin D (10 μ g/ml) was added, incorporation was reduced to 0.6%. The in vitro product was RNase-sensitive. The RNA sedimented product was as large as 30S; about 50% was between 18S and 28S. These RNA chains corresponded to strands that had been initiated in vivo and to chains that were longer than the polyoma genome size synthesized de novo. Approx 95% of this RNA was viral. Approx 12% to 15% of the RNA was transcribed from the E strand, 85% to 88%, from the L strand. The product also contained self-annealing complementary sequences. (42 refs.)

- 77-6979 **Virus-specific Proteins in the Plasma Membrane of Cells Lytically Infected or Transformed by Polyoma Virus.** (Eng) Ito, Y. (Dept. Cell Regulation, Imperial Cancer Res. Fund Labs., Lincoln's Inn Fields, London WC2A 3PX, England); Brocklehurst, J. R.; Dulbecco, R. *Proc Natl Acad Sci USA* 74(10): 4666-4670; 1977.

Antisera (raised in rats) containing specificities directed against the tumor antigen of polyoma virus also reacted with several proteins in the plasma membrane of mouse cells infected with the virus. The main component has an apparent mol wt of 55,000. The appearance of this protein after infection with early temperature-sensitive A mutants was temperature-dependent, like the tumor antigen itself. Pulse-chase isotope experiments suggested that this protein originated from a precursor, perhaps by cleavage; its production appeared to be facilitated by the A mutation. Two other components with apparent mol wt of 61,000 and 28,000 were also present, but they were more variable from experiment to experiment. All proteins were absent from the plasma membranes of cells infected with a transformation-defective mutant, NG-18. Up to four virus-specific proteins could be isolated from the plasma membranes of rat, hamster, and mouse cells transformed by the virus. The possible role of the plasma membrane proteins in cell transformation is discussed. (44 refs.)

- 77-6980 **Cancer-associated Serum Galactosyltransferase Activity: Demonstration in an Animal Model System.** (Eng) Podolsky, D. K. (Dept. Medicine, Harvard Medical Sch., Boston, MA 02114); Weiser, M. M.; Westwood, J. C.; Gammon, M. *J Biol Chem* 252(5): 1807-1813; 1977.

Two solid tumor lines were produced in outbred hamsters by sc injection of polyoma (py)-transformed baby hamster kidney (BHK) cells. Tumor growth correlated with the appearance in serum of an electrophoretically distinct peak of galactosyltransferase: SGF-fetuin acceptor activity on polyacrylamide gels (ie, fetuin minus terminal sialic acid and galactose). This slow-moving peak of enzyme activity (GT-II-H) was detected before the tumor could be seen, and the amount of activity in the peak was linearly related to tumor growth. GT-II-H was not detectable in control animals, and it separated from a faster migrating serum galactosyltransferase activity (GT-I-H) found in the sera of control and tumor-bearing hamsters. These two activities maintained their respective mobilities on reelectrophoresis. Solubilized enzyme from excised tumor had an electrophoretic mobility identical to that of GT-II-H in sera from tumor-bearing animals. In contrast, enzyme activity solubilized from livers of control or tumor-bearing hamsters showed a mobility similar to that of GT-I-H. Medium derived from nonconfluent py-transformed BHK cells in tissue culture contained galactosyltransferase activity that coelectrophoresed with the slower

migrating GT-II-H in sera of tumor-bearing animals. The kinetic properties of the two enzymes were similar, except that the uridine diphosphates-galactose of GT-II-H (1.0×10^{-5} M) was half that of GT-I-H (2.0×10^{-5} M). (25 refs.)

77-6981 Quantitative Electronic Analysis of Normal and Transformed BHK21 Fibroblast Aggregation.

(Eng) Whur, P. (Cell Biology Unit, Marie Curie Memorial Foundation, Oxted, Surrey, England); Koppel, H.; Urquhart, C.; Williams, D. C. *J Cell Sci* 23: 193-209; 1977.

The aggregation of normal and transformed BHK21 cells was analyzed quantitatively by using a Coulter counter coupled to a particle size discriminator. BHK21 C13 cells and polyoma virus-transformed BHK21 Py6 cells were suspended by treatment of heavy trypsin/EDTA and then aggregated at 37°C. Plots were obtained showing the distribution of cells in 1-50 cell aggregates, and the rates of redistribution of cells between aggregates were calculated. The initial single cell suspension of BHK21 C13 cells contained only 44% of single cells. During the first 5 min of aggregation single cells and aggregates containing up to 4 cells disappeared into larger aggregates. Adhesions between single cells were the most common event throughout aggregation, but these declined relatively rapidly with time as adhesions between aggregates became more prominent. The overall rate of adhesions declined 10-fold within 12 min and 100-fold within 90 min. Heavy trypsin/EDTA treatment of normal cells released DNase-sensitive material which altered the aggregation kinetics. These changes included the disaggregation of small, loosely adhering cell clusters coupled with the formation of abnormally large aggregates. Nearly all BHK21 Py6 cells (92%) in initial suspensions were single, and by 30 min few single cells had adhered to form aggregates. During the first 5 min, the rate of loss of single cells was 25% that of normal BHK cells. The formation rate of aggregates was very slow and declined markedly with increasing size; this reflects the lower adhesiveness of BHK21 Py6 cells, which is initially about 15% that of normal cells. (21 refs.)

77-6982 Uniform Representation of the Human Papovavirus BK Genome in Transformed Hamster Cells. (Eng.) Howley, P. M. (Lab. Pathology, NCI, Bethesda, MD 20014); Martin, M. A. *J Virol* 23(1): 205-208; 1977.

Hamster kidney cells transformed by human papovavirus BK (BKV) were found to contain a uniform representation of the viral genome in multiple copies. The viral DNA content of each of three individual cloned cell lines (BK-HK-2, BK-HK-3, BK-HK-6) was determined by studying the effect of unlabeled BKV-transformed cell DNA on the rate of reannealing of radiolabeled BKV DNA. The equivalents of viral DNA per diploid genome ranged from 2.7 to 5.3. That the

BKV genome was uniformly present was determined by reassociation of each of the four restriction endonuclease (*R. Hind* III) fragments of the BKV DNA in the presence of unlabeled DNA from HK-BK-3 cells. The restriction fragments *Hind* III-A, *Hind* III-B, *Hind* III-C, and *Hind* III-D were represented at 5.7, 4.1, 5.8, and 5.7 copies per diploid genome equivalent, respectively. This variance was not considered significant, and it was concluded that the four BK *Hind* III fragments are equally represented in HK-BK-3. These cells were in early passage (approx 12), in contrast to the long passage history of SVT2 cells (derived from mouse BALB/3T3 cells transformed by simian virus 40), in which the SV40 genome has been reported to be unequally represented. (15 refs.)

77-6983 Differential Neurooncogenicity of Strains of JC Virus, a Human Polyoma 1Virus, in Newborn Syrian Hamsters. (Eng) Padgett, B. L. (Dept. Medical Microbiology, Univ. Wisconsin Medical Sch., Madison, WI 53706); Walker, D. L.; Zur Rhein, G. M.; Varakis, J. N. *Cancer Res* 37(3): 718-720; 1977.

The neurooncogenicity of three recently isolated strains of JC virus, a human polyoma virus, was determined by intracerebral inoculation of newborn Syrian golden hamsters with 0.02 ml of virus. All three strains produced malignant brain tumors in most inoculated hamsters during a 6.5-mo observation period. The results obtained with the MAD-2 strain, cerebellar medulloblastomas in 19/20 animals and pineal gland tumors in 0/20 animals, were similar to those observed previously with the prototypic JC strain, MAD-1. The MAD-4 strain, however, induced pineal gland tumors in 10/22 animals but cerebellar tumors in only 10/22. The MAD-3 strain was neurooncogenic, but too few animals survived to provide significant information. The basis for the apparent predilection of the MAD-4 strain for the pineal gland is unknown. Two hamsters, one inoculated with MAD-2 and the other with MAD-4, developed extracranial neuroblastomas. (11 refs.)

77-6984 JC Virus, a Human Polyomavirus Associated with Progressive Multifocal Leukoencephalopathy: Additional Biological Characteristics and Antigenic Relationships. (Eng) Padgett, B. L. (Dept. Medical Microbiology, Univ. Wisconsin Medical Sch., Madison, WI 53706); Rogers, C. M.; Walker, D. L. *Infect Immun* 15(2): 656-662; 1977.

JC virus, a human polyomavirus, failed to grow or produce cytopathic effects in cells other than primary human fetal glial (PHFG) cells. Cells tested included other primary human cells and monkey, hamster, mouse, and mink glial cells. Only a few cells in inoculated susceptible human cell cul-

tures produced T or virion antigen. In PHFG cell cultures, JC virus produced subtle cytopathic effects, and the majority of the progeny remained cell-associated. Few cells in the heterogeneous PHFG cell cultures contained T antigen at 24 hr postinoculation, and virion antigen was not detected until 48 hr postinoculation. The infectivity of JC virus was resistant to inactivation by ether and by heating at 50 C for 1 hr. A three-way minor antigenic relationship was demonstrated among the virion antigens of JC virus, BK virus, and simian virus 40 (SV40) by neutralization and/or hemagglutination inhibition tests. Serological evidence is presented for the existence of JC virus as a distinct entity before the use of SV40-contaminated poliovirus vaccines and for the nonexistence of an animal reservoir for JC virus infection. (19 refs.)

- 77-6985 Binding of Adenovirus to Microtubules. II. Depletion of High-Molecular-Weight Microtubule-associated Protein Content Reduces Specificity of In Vitro Binding.** (Eng) Weatherbee, J. A. (Worcester Foundation for Experimental Biology, Shrewsbury, MA 01545); Luftig, R. B.; Weihing, R. R. *J Virol* 21(2): 732-742; 1977.

The effect of a high-mol-wt microtubule (MT)-associated protein (MAP) on the in vitro binding of adenovirus particles to the brain MT of rats and 1- to 3-day-old chicks was investigated. Fractionation of purified chick brain MT resulted in two major peaks. The MAP's were mainly present in peak 1 -- the material from peak 1 polymerized readily at protein concentrations of 1.5 to 2.5 mg/ml to produce an abundant number of MT. The material from peak 2 gave fewer MT, but sufficient numbers were present to measure their virus-binding properties. Two methods of measuring adenovirus type 5 binding were used. With the material from peak 1, 89.4% and 83.6%-87.6% of the virus was bound to the edge of the MT; with that from peak 2, 62.5%-64.7% and 54.2%-63.4% was bound, respectively. With the unfractionated MT, almost all the virus particles were associated with the edges of the MT, similar to peak 1 MT, but with peak 2 MT, the association with adenovirus particles was more random, and more viruses were noted lying on top of the MT. When polymerized chick brain MT were treated with trypsin, most of the MAP's were removed without destruction of the tubulin or the structural integrity of the MT. This treatment also abolished specific virus-binding activity. The corrected specific binding of adenovirus particles to unfractionated MT was at least two to three times higher than the binding to MT that have had their MAP concentrations depleted by chromatography or trypsin treatment. These findings are consistent with the suggestion that the association between adenovirus and MT is mediated by MAP's. (25 refs.)

- 77-6986 Isolation of the Viral DNA Replication Complex from Adeno-associated Virus Type 1-infected Cells.** (Eng) Handa, H. (Lab. Experimental Pathology,

Natl. Inst. Arthritis, Metabolism, and Digestive Diseases, Bethesda, MD 20014); Shimojo, H. *J Virol* 24(2): 444-450; 1977.

The adeno-associated virus type 1 (AAV-1) DNA replication complex was isolated from human embryonic kidney cell coinfecting with AAV-1 and the temperature-sensitive mutant of human adenovirus type 5 (H5ts125) at 40.5 C, to establish an in vitro system for AAV DNA replication. After the replication complex was solubilized, RNase inhibited DNA synthesis, suggesting the involvement of RNA synthesis in DNA synthesis. The complex sedimented with a mean size of 23S, but it sedimented in alkaline sucrose as smaller molecules than AAV DNA (14.4S). This suggests that the complex lacks factors necessary for the formation of complete molecules. The complex was not formed in cells infected with AAV-1 alone. It synthesized AAV DNA exclusively, as indicated by hybridization and sedimentation in neutral sucrose. (27 refs.)

- 77-6987 Visualization and Mapping of Late Nuclear Adenovirus RNA.** (Eng) Meissner, H. C. (Lab. Molecular Genetics, Natl. Inst. Child Health and Human Development, Bethesda, MD 20014); Meyer, J.; Maizel, J. V.; Westphal, H. *Cell* 10(2): 225-235; 1977.

The nuclei of KB cells harvested late during productive infection with adenovirus type 2 (Ad2) contained RNA molecules measuring up to 13 μ m in length, as determined by electron microscopy of denatured RNA. Some of the molecules had the secondary structure characteristic of precursor ribosomal RNA, but others showed almost no intramolecular folding. When hybridized to double-stranded viral DNA under conditions favoring RNA:DNA duplex formation, nuclear AD2 RNA displaced the homologous DNA region and generated R-loop structures whose size was proportional to the length of the hybridizing RNA. Slowly sedimenting RNA formed small R loops, but the RNA of high sedimentation velocity generated loops that spanned a large proportion of the DNA length. Many of the R loops were oriented on the conventional Ad2 map by using the simian virus 40 (SV40) sequences within a nondefective Ad2:SV40 hybrid virus as a marker. The analysis was restricted to the most abundant sequences of late Ad2 nuclear RNA participating in R-loop formation. A small but significant proportion of large RNA generates loops between map positions 0.3 and 0.9. The more frequent RNA of intermediate size hybridizes with midpoints near map positions 0.55 and 0.88, ie, near the gene locations for hexon and fiber. These findings are compatible with the idea that nuclear RNA's are intermediates in a processing pathway leading to mature forms of late Ad2 messenger RNA. (45 refs.)

- 77-6988 Analysis of DNA from Adenovirus 12-transformed Cells for Virus-specific DNA Sequence with Viral DNA Fragments Cleaved with Restriction**

Endonuclease. (Eng) Yano, S. (Dept. Molecular Biology, Cancer Res. Inst., Sapporo Medical Coll., Minami-1-jo, Nishi-17-chome, Chuo-ku, Sapporo 060, Japan); Tsuchida, N.; Fujinaga, K. *Gann* 68(1): 107-114; 1977.

EndoR HindIII-cleaved DNA fragments of adenovirus 12 (Ad12) DNA were used as probes to detect Ad12 viral genomes in Ad12-transformed hamster embryo cells. In all DNA fragments except fragment B, reassociation gave a linear plot. More than 77% of the viral genome nucleotide sequence was present in the infected cells, with 5 to 10 copies/haploid quantity of cell DNA occurring in each of the 11 fragments examined (A, C-L). The reassociation kinetics of fragment B deviated from second order kinetics, suggesting that only part of the fragment may be present in the cell DNA. Since most if not all of the Ad12 genome is present in the transformed cells, it is suggested that either part of the viral sequences or whole parts of these sequences are transcribed and processed in these cells. (24 refs.)

77-6989 Hepatitis B Virus Infection and Primary Hepatocellular Carcinoma. (Eng) Tabor, E. (Div. Blood and Blood Products, Bureau Biologics, Food and Drug Admin., Bldg. 29, 8800 Rockville Pike, Bethesda, MD 20814); Gerety, R. J.; Vogel, C. L.; Bayley, A. C.; Anthony, P. P.; Chan, C. H.; Barker, L. F. *J Natl Cancer Inst* 58(5): 1197-1200; 1977.

Serum samples from primary hepatocellular carcinoma (PHC) patients in Uganda (47), Zambia (19), and the US (27) were examined for evidence of hepatitis B virus (HBV) infection. The sera were tested for HBV surface antigen (HBsAg) and its antibody (anti-HBs), antibody to the HBV core antigen (anti-HBc), and HBV e antigen (HBeAg) and its antibody. Active HBV infection, as indicated by positive tests for HBsAg (with or without anti-HBs) and anti-HBc (without anti-HBs), was present in 62% of the PHC patients, in contrast to 10% of the African controls and < 1% of most adult Americans. HBeAg, which is associated with chronic persistent and chronic aggressive hepatitis, was rare among patients and controls. (35 refs.)

77-6990 A New Cell Line from a Human Chondrosarcoma. (Eng) de Man, J. C. (Pathology Lab., Univ. Leiden, Leiden, Netherlands); Snoep, M. P.; Huiskens-v. d. Meij, J. W.; Warnaar, S. O.; Schaberg, A. *Br J Cancer* 35(4): 403-414; 1977.

The morphology and growth characteristics of a cell line derived from a chondrosarcoma removed from a 65-yr-old man are presented. Most of the cultured cells had an epithelioid appearance, and the nuclei had 2-11 nucleoli. Multinucleate giant cells with up to 10 nuclei were also present. Between passages 9 and 60, the chromosome numbers ranged from 63

to 85; a Y chromosome was present in > 90% of the metaphases, and, occasionally, cells with large numbers of chromosomes contained 2 or 3 Y chromosomes. Biochemically, the cells contained particles with a density of 1.16, with cores of density 1.23 that were associated with a reverse transcriptase-like enzyme and with 70S RNA. The cells contained cross-reacting antigens with known animal oncornaviruses. Electron microscopy of the cells failed to reveal virus particles, but virus-like particles could be identified in the culture medium. The population doubling time was estimated at 2 days. Injection of the tumor cells into irradiated hamsters and nude mice did not result in tumor formation. (21 refs.)

77-6991 Unusual Prevalence of Epstein-Barr Virus Early Antigen (EBV-EA) Antibodies in Ataxia Telangiectasia. (Eng) Joncas, J. (Dept. Virology, Institut Armand-Frappier, Pediatric Res. Center, Ste-Justine Hosp., Montreal, Province of Quebec, Canada); Lapointe, N.; Gervais, F.; Leyritz, M. *J Immunol* 119(5): 1857-1859; 1977.

Antibodies to Epstein-Barr virus early antigen (EBV-EA) were demonstrated in 8/16 ataxia telangiectasia (AT) patients and in 8/42 unaffected relatives. This high prevalence of EA antibodies may have been partly due to recent infection, since two patients and one family member had viral capsid antigen antibodies but lacked EBV nuclear antigen (EBNA) antibodies, the characteristic pattern of recent infection. Alternatively, AT patients may fail to produce EBNA antibodies as a result of their immunodeficiency. The significance of persisting EA antibodies in relation to tumor development is discussed. (16 refs.)

77-6992 Viral Protein Synthesis by Tissues from Avian Leukosis Virus-infected Chickens. I. Susceptible Chickens Infected after Hatching. (Eng) Welt, S. (Dept. Pathology, New York Univ. Sch. Medicine, 550 First Ave., New York, NY 10016); Purchase, H. G.; Thorbecke, G. J. *J Immunol* 119(5): 1800-1805; 1977.

Susceptible line 15I chickens were infected at hatching with avian leukosis virus. Viral protein synthesis was detected by ¹⁴C-amino acid incorporation into these proteins by tissues in vitro, as shown by autoradiography of viral group-specific (gs) protein immunoelectrophoretic patterns. Synthesis of proteins p27, p15, and p12 was first detected in the thymus, spleen, bursa, liver, kidney, testis, ovary, and lung of 18-day-old chickens. The synthesis continued up to age 7 to 9 wk, but at 10 wk it was detected only in the lung and genital organs. Grossly leukotic chickens showed gs protein synthesis primarily in the bursa and spleen but, depending on the degree of leukotic infiltration, also in the liver and kidney. Tissues from uninfected controls showed no gs protein synthesis. The results indicate that all tissues tested produced virus during the initial viremic stage of the disease, but that

lymphoma cells were predominant in viral protein synthesis during the leukotic stage. Enhanced IgG synthesis in spleen tissue from infected chickens during the viremic stage suggested the presence of a humoral immune response to the virus. Leukotic tissue appeared to produce both IgM and IgG. (31 refs.)

- 77-6993 **Solubilization of the Epstein-Barr Virus-determined Nuclear Antigen and Its Characterization as a DNA-binding Protein.** (Eng) Luka, J. (Dept. Tumor Biology, Karolinska Inst., S 104 01 Stockholm 60, Sweden); Siegert, W.; Klein, G. *J Virol* 22(1): 1-8; 1977.

Epstein-Barr virus (EBV) nuclear antigen (EBNA) was solubilized from the isolated nuclei of two EBV-transformed cell lines, Raji and AW-Ramos, by high-salt treatment. Its DNA-binding properties were studied by DNA-cellulose chromatography and a ^{51}Cr -release complement fixation assay. EBNA bound to both double and single-stranded calf thymus DNA, but it showed a higher affinity for double-stranded DNA. There was no detectable difference in the DNA binding of EBNA prepared from Raji and AW-Ramos cells. (40 refs.)

- 77-6994 **Transient Induction of a Nuclear Antigen Unrelated to Epstein-Barr Nuclear Antigen in Cells of Two Human B-Lymphoma Lines Converted by Epstein-Barr Virus.** (Eng) Fresen, K. O. (Institut für klinische Virologie der Universität Erlangen-Nürnberg, Loschgestrasse 7, 852 Erlangen, W. Germany); zur Hausen, H. *Proc Natl Acad Sci USA* 74(1): 363-366; 1977.

Studies were conducted to characterize a transiently induced nuclear antigen (TINA) identified in the cells of two human B-lymphoma lines converted by Epstein-Barr virus (EBV) and the associated serological response in various groups of patients. Infection of cells of the EBV-negative human B-lymphoma lines BJAB and Ramos with EBV preparations converted these cells to EBV genome carriers expressing Epstein-Barr nuclear antigen (EBNA) in almost 100% of the cells. Induction of these cells as well as clones from EBV-converted BJAB cells with iododeoxyuridine, aminopterin, and hypoxanthine resulted in the appearance of TINA in about 1% to 6% of the cells 1-4 days after induction. This antigen is different from known EBV-induced antigens such as EBNA, viral capsid antigen (VCA), or the D- and R-subspecificities of the early antigen (EA) complex. All sera with TINA reactivity tested thus far also reacted highly with EBV VCA and EA. This relationship was unidirectional, as not all sera with high VCA and EA titers also contained detectable antibodies against TINA. Among 200 sera tested, TINA reactivity was most frequently observed in sera of patients with nasopharyngeal carcinoma (7/29). It was also observed in sera of the only two patients with immunoblastoma

tested and, occasionally, in sera from patients with Hodgkin's disease and chronic lymphatic leukemia. TINA reactivity was observed in 3/70 sera from nontumor patients: 2 patients suffered from chronic infectious mononucleosis and the other had persistent splenomegaly. Several possibilities are advanced concerning the nature of TINA: (1) a new EBV-induced antigen; (2) a fetal antigen; (3) an antigen of an EBV-related but different herpesvirus present in BJAB and Ramos cells; or (4) an antigen of a virus totally different from EBV. It is presently impossible to decide which of these alternatives may be correct. (12 refs.)

- 77-6995 **A Solid-Phase Radioimmunoassay for Epstein-Barr Virus-associated Membrane Antigen Prepared from B95-8 Cell Culture Supernatants.** (Eng) Dolken, G. (Dept. Tumor Biology, Karolinska Inst., S-104 01 Stockholm 60, Sweden); Klein, G. *J Natl Cancer Inst* 58(5): 1239-1245; 1977.

Epstein-Barr virus (EBV)-associated membrane antigen (MA) was concentrated from B95-8 cell culture media by precipitation with polyethylene glycol followed by chromatography on Bio-Gel A-50m. In a Raji cell-binding assay, MA-positive material was found only in the void volume of the column. After ultracentrifugation, all antigenic activity appeared in the pellet, which suggested that MA was present in aggregates, presumably fragments of cellular membranes and/or virus envelopes. The MA-containing preparation was photopolymerized in polyacrylamide gel. The homogenized gel was used in a solid-phase radioimmunoassay with ^{125}I -labeled IgG from an anti-MA positive reference serum and an anti-MA negative control serum. The specificity of the reaction was confirmed in blocking tests with anti-EBV positive and negative sera. The results of the radioimmunoassay correlated well with those of direct immunofluorescence tests for MA. The radioimmunoassay showed the existence of at least two subspecificities of the MA complex. (28 refs.)

- 77-6996 **Isolation of Infectious EB Virus from the Epithelial Tumour Cells of Nasopharyngeal Carcinoma.** (Eng) Trumper, P. A. (Dept. Pathology, Univ. Bristol Medical Sch., Univ. Walk, Bristol BS8 1TD, England); Epstein, M. A.; Giovannella, B. C.; Finerty, S. *Int J Cancer* 20(5): 635-662; 1977.

Evidence of herpesvirus replication was found by light and electron microscopy in the malignant epithelial cells of 2/6 pharyngeal carcinomas (NPC) examined directly after growth in nude mice to eliminate nonmalignant infiltrating cells. The agent was identified as Epstein-Barr virus (EBV) by immunofluorescence tests for EBV capsid antigen, and it was shown to be biologically active by its ability to infect and transform fetal cord blood lymphocytes. Lymphoblastoid cell lines that express EBV nuclear antigen were established from

the transformed fetal lymphocytes; they carry the first virus isolate from the actual epithelial tumor cells of NPC, in a form suitable for further investigation. The results are discussed in terms of the relationship of EBV to NPC epithelial cells. (46 refs.)

77-6997 **Viral Particles in Nasopharyngeal Carcinoma.** (Eng) Nadol, J. B. (Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114). *Laryngoscope* 87(11): 1932-1937; 1977.

The case report of a 17-yr-old man with lymphoepithelioma of the nasopharynx and Epstein-Barr virus titers of 1:3,200 is presented. Electron microscopy revealed viral particles in the cytoplasm of the malignant epithelial cells. Less than 1% of the tumor cells contained these particles, but the exact incidence was not determined. The most common particle was a nucleocapsid measuring 75 to 100 nanometers in diameter. The viral particles were indistinguishable from those in tissue cultures of Burkitt's lymphoma and nasopharyngeal carcinoma, and they had the same morphological characteristics as herpesvirus. There was no direct evidence that these particles are Epstein-Barr virus, but the presence of assembled virus particles in the tumor cells greatly strengthens the more indirect morphological data associating Epstein-Barr virus with human cancer. (18 refs.)

77-6998 **Epstein-Barr Virus Genome Studies in Burkitt's and Non-Burkitt's Lymphomas in Uganda.** (Eng) Olweny, C. L. (Uganda Cancer Inst., Post Office Box 3935, Kampala, Uganda); Atine, I.; Kaddu-Mukasa, A.; Owor, R.; Andersson-Anvret, M.; Klein, G.; Henle, W.; de The, G. *J Natl Cancer Inst* 58(5): 1191-1196; 1977.

Ugandan lymphoma patients were tested for Epstein-Barr virus (EBV)-specific nuclear antigen (EBNA) and EBV DNA by immunofluorescence and nucleic acid hybridization techniques, respectively. Biopsy tissue from 27/34 Burkitt's lymphoma (BL) patients were EBNA-positive, compared with 0/25 non-BL tissues. Of 15 BL tumors, 14 were positive for EBV DNA, with a mean of 39 EBV genome equivalents/cell. Each of the 15 non-BL specimens tested had a < 2 virus genome equivalents/cell, although all the patients had serologic evidence of past EBV infection. These results support the possible etiologic role of EBV in African BL. (32 refs.)

77-6999 **Activation of Epstein-Barr Virus in Hybrid Cells.** (Eng) Tsang, K. Y. (Dept. Surgery, Medical Coll. Ohio, C. S. 10008, Toledo, OH 43614); Hann, W. D. *J Natl Cancer Inst* 58(5): 1295-1301; 1977.

Human-primate hybrid cell lines were established by fusion of African green monkey kidney cells (Vero) with lymphoblastoid cells from patients with infectious mononucleosis (IMK101) and from a Burkitt's lymphoma culture (HR1K). Both Epstein-Barr virus (EBV)-specific antigens and EBV particle-containing cells increased in the hybrid lines (IMK101/Vero, HR1K/Vero). Treatment of the hybrids with 5-bromodeoxyuridine induced more antigen-positive and more virus-containing cells. EBV could be activated from IM lymphoblastoid cells by fusion of the lymphoblastoid cells with the Vero cells. The increase of viral antigens and virus particles may have been due to the cellular interaction between Vero cells and the lymphoblastoid cells or to a possible derepressor supplied by the Vero component of the hybrid. Virus derived from the HR1K cell line replicated in the human-primate hybrid, but further investigation may be necessary to determine if it was identical to the EBV derived from the human cell line. (36 refs.)

77-7000 **Identification of Virion Polypeptides in Hamster Cells Transformed by Herpes Simplex Virus Type 1.** (Eng) Gupta, P. (Dept. Microbiology, Milton S. Hershey Medical Center, Pennsylvania State Univ., Coll. Medicine, Hershey, PA 17033); Rapp, F. *Proc Natl Acad Sci USA* 74(1): 372-374; 1977.

Polypeptides present on the surface of herpes simplex virus type 1 (HSV-1) virions were identified, and their presence in hamster cells transformed by HSV-1 was investigated. At least six major and four minor proteins were detected on the surface of the virion by analysis of surface-labeled virus (using ¹²⁵I) in the presence of lactoperoxidase and H₂O₂. All major surface proteins were glycosylated, as indicated by their capacity to bind concanavalin A. Surface-labeled HSV-1 envelope antigen was reacted with increasing concentrations of rabbit antiserum against a tumor derived by the injection of HSV-1-transformed cells into a syngeneic hamster. Polyacrylamide gel electrophoresis of the immunoprecipitate indicated the presence of three major virion proteins in the tumor. Since the tumor was derived by injecting an HSV-1-transformed cell line into a hamster, it is concluded that the transformed cells must also contain these three proteins. (14 refs.)

77-7001 **Replication of Herpes Simplex Virus DNA after Removal of Hydroxyurea Block from Infected Cells.** (Eng) Shlomai, J. (Lab. Molecular Virology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Becker, Y. *J Gen Virol* 37(2): 429-433; 1977.

Treatment of BSC-1 cells infected by herpes simplex virus (HSV) type 1 with hydroxyurea (HU) markedly inhibited the synthesis of virus DNA. Compared with untreated infected cells, only 0.36% of the ³H-thymidine label was incorporated into virus DNA in the presence of HU. Removal of HU re-

sulted in a renewed synthesis of virus DNA as determined by the gradual increase in ^3H -thymidine incorporation into HSV DNA. The labeled virus DNA molecules were isolated and chromatographed on benzoylated naphthoylated DEAE (BND)-cellulose columns to separate the replicative intermediates that have single-stranded (ss) sequences from the mature double-stranded (ds) DNA genomes. Mature radioactive dsDNA molecules appeared 22 min after HU was removed and then gradually increased in amount. The virus DNA molecules synthesized during the initial 20 min after HU removal constituted the replicative intermediates of HSV DNA. HSV DNA synthesis was calculated to proceed at about 5×10^6 daltons/min. (13 refs.)

77-7002 Common Precursor Pathways of Herpes DNA and of Repair Synthesis in Ultraviolet Irradiated Cells. (Eng) Coppey, J. (Fondation Curie-Institut du Radium, Section de Biologie, 26, rue d'Ulm, 75321 Paris Cedex 05, France). *Nature* 265(5591): 260-262; 1977.

CV-1 cells were infected by herpes simplex virus (HSV) type 1 and irradiated with UV light to study the common precursor pathways of HSV replication and DNA repair synthesis in UV-irradiated cells. Inhibitors of endogenous DNA synthesis such as fluorodeoxyuridine, cytosine arabinoside, and hydroxyurea are less effective on (1) HSV replication in UV-irradiated cells than in control cultures and (2) incorporation of the four deoxyribonucleosides into cellular DNA during post-UV DNA synthesis than during normal synthesis. Thus, deoxyribonucleoside precursors of DNA synthesis are supplied essentially by exogenous pathways in post-UV DNA synthesis and by exogenous and endogenous pathways in normal CV-1 cells. A similar pattern appears to occur for DNA synthesis of HSV grown in UV-irradiated CV-1 cells, compared with virus grown in control cells. (27 refs.)

77-7003 The Tumor Enhancing Property of Herpes Simplex Virus Type-2 (HSV-2). (Eng) Reiss-Gutfreund, R. J. (Inst. Cancer Res., Univ. Vienna, Borschkegasse 8 a, A-1090 Vienna, Austria); Dostal, V.; Binder, M.; Letnansky, K. *Osterr Z Onkol* 3(5/6): 148-154; 1977.

The tumor-enhancing properties of herpes simplex virus type 2 (HSV-2) were studied in a syngeneic methylcholanthrene (MC)-induced tumor system in DBF-1 mice. One group of mice was inoculated sc with 0.1 ml of a HSV-2 virus suspension (containing 2.5×10^3 plaque-forming units) simultaneously with 1×10^5 tumor cells im. Another group of mice (controls) was treated with an intact CV-1 cell culture supernatant and 1×10^5 tumor cells. The first palpable tumors appeared on day 6 in the virus-treated group and on day 9 in the control group. More tumors were formed in the virus-treated group (75%) than in the controls (40%). Tumor proliferation could be modulated depending upon the number

of tumor cells implanted and the chronological relationship of tumor cell injection to virus injection. There was no difference between the two groups when the tumor cell dose was increased to advance the first appearance of tumors to < 6 days or when the tumor cells were implanted 3 days before virus injection. Previous in vitro mixing of the tumor cells with virus completely prevented tumor formation, probably because of their lysis by the virus. A similar situation probably occurs in mice that die before the 13th day after infection; ie, the tumor cells are destroyed by the virus. It appears that acute HSV-2 infection prevents the induction of sarcomas by MC, but latent infection promotes their growth. Tumor enhancement due to infection with HSV-2 may be caused by immunosuppression or by a mitogenic effect triggered by infection. (24 refs.)

77-7004 Inhibition of *Herpesvirus saimiri* Replication by Phosphonoacetic Acid, Benzo(a)pyrene, and Methylcholanthrene. (Eng) Pearson, G. R. (Mayo Medical Sch., Mayo Foundation, Rochester, MN 55901); Beneke, J. S. *Cancer Res* 37(1): 42-46; 1977.

The effects of benzo(a)pyrene (BP) and 3-methylcholanthrene (3-MC) on *Herpesvirus saimiri* replication were investigated and compared with those of phosphonoacetic acid (PAA). PAA inhibited the synthesis of virus-induced intracellular late antigens, membrane antigens, and infectious virus but not the synthesis of the early antigens induced by *H. saimiri*. In contrast, BP and 3-MC inhibited primarily membrane antigen expression and infectious virus production. BP was the most effective of the two compounds, with significant inhibition occurring with $2 \mu\text{g}/\text{ml}$; a minimum concentration of $10 \mu\text{g}/\text{ml}$ was required with 3-MC. Both compounds were most effective when present continuously during the 4-day infection process. However, exposure of infected cultures to a 3-hr pulse with each chemical also inhibited membrane antigen expression. Furthermore, treatment of cells for 48 hr before virus infection inhibited membrane antigen expression but not that of early or late antigens. These results demonstrate that some chemical carcinogens are capable of altering the *H. saimiri* replication cycle by inhibiting some but not all late events. (27 refs.)

77-7005 Differentiation of D-Type Virus from Continuous Human Cells (Il'in-Bykovskii Virus) and Mason-Pfizer Monkey Virus by Virus Envelope Antigens. (Rus) Il'in, K. V. (N. F. Gamaleia Inst. Epidemiology and Microbiology, Acad. Medical Sciences USSR, Moscow, USSR); Kriukova, I. N. *Biull Eksp Biol Med* 34(8): 208-210; 1977.

Il'in-Bykovskii Virus (IBV, D-Type oncornavirus) was differentiated from Mason-Pfizer monkey virus (M-PVM) by immunautoradiographic immunodiffusion and virus neu-

neutralization tests. The viruses were cultivated in autologous human embryo cell cultures, and the cells were infected with cell-free virus-containing material. Virus-neutralizing antisera were obtained from rabbits immunized with purified IBV and from goats immunized with M-PMV. The results of the virus neutralization test were determined by the presence or absence of group-specific antigen in the infected cells. The antiserum to M-PMV envelope antigen did not neutralize the IBV antigen. It is concluded that IBV and M-PMV differ from each other by their envelope antigens and that they should be regarded as different viruses. (16 refs.)

77-7006 Purification and Characterization of Baboon Endogenous Virus DNA Polymerase. (Eng) Sabin, P. S. (Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD 20014); Friedman, B.; Gallo, R. C. *Biochim Biophys Acta* 479(2): 198-206; 1977.

An RNA-directed DNA polymerase was purified from baboon endogenous C-type virus by successive column chromatography on diethylaminoethylcellulose, phosphocellulose, and hydroxyapatite. The purified DNA polymerase has a mol wt of 68,000, a pH optimum of 8.0, a Mn^{2+} optimum of 1 milliM, and a KCl optimum of 40 milliM. The purified enzyme transcribes heteropolymeric regions of viral 60S-70S RNA isolated from different C-type viruses. The purified enzyme is immunologically related to a similarly purified polymerase from the cat endogenous C-type virus RD114. (28 refs.)

77-7007 Biochemical and Immunological Properties of gag Gene-coded Structural Proteins of Endogenous Type C RNA Tumor Viruses of Diverse Mammalian Species. (Eng) Stephenson, J. R. (Lab. RNA Tumor Viruses, NCI, Bethesda, MD 20014); Reynolds, R. K.; Devare, S. G.; Reynolds, F. H. *J Biol Chem* 252(21): 7818-7825; 1977.

The biochemical and immunological properties of gag gene translational products of mammalian C-type viruses from mice, cats, pigs, baboons, woolly monkeys, and gibbon apes were compared. The analogous gene products in the different species were identified, and a map of the gag coding for viral proteins for each of the major groups of mammalian RNA tumor viruses was constructed. (38 refs.)

77-7008 Characterization of SA12 as a Simian Virus 40-related Papovavirus of Chacma Baboons. (Eng) Valis, J. D. (Dept. Pathobiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD 21205); Newell, N.; Reissig, M.; Malherbe, H.; Kaschula, V. R.; Shah, K. V. *Infect Immun* 18(1): 247-252; 1977.

SA12 virus was identified as a new papovavirus of the simian virus 40-polyoma (SV40) subgroup. The chacma baboon

was identified as its probable natural host even though the virus was originally isolated from an uninoculated South African vervet monkey kidney culture. T antigens of SA12 and SV40 viruses were strongly and reciprocally cross-reactive. Sera from chacma baboons and, to a lesser extent, vervet monkeys had neutralizing antibodies to SA12 virus. (16 refs.)

77-7009 Polypeptide Synthesis in Simian Virus 5-infected Cells. (Eng.) Peluso, R. W. (Rockefeller Univ., New York, NY 10021); Lamb, R. A.; Choppin, P. W. *J Virol* 23(1): 177-187; 1977.

Polypeptide synthesis was examined in simian virus 5 (SV5)-infected bovine kidney cells (MDBK), monkey kidney cells (TC7 clone of CV-1 cells), and primary cultures of chicken embryo fibroblasts (CEF). All the known virion polypeptides were synthesized in infected cells in unequal amounts, in proportions similar to those found in virions, suggesting that their synthesis rates are controlled. In infected MDBK cells, polypeptides I, II, IV, and V, with apparent mol wts of 99,000, 97,000, 78,000, and 27,000, respectively, were also evident. The synthesis of these cellular polypeptides may be enhanced in infected cells. Infected CEF cells produced polypeptide III (mol wt 86,000) in addition to I, II, IV, and V and the viral proteins. Infected CV-1 cells synthesized the viral proteins and polypeptides IV and V. Polypeptides I-IV, which are thought to be host polypeptides whose synthesis is enhanced after viral infection, may play a role in virus replication, and polypeptide V may be a virus-specific, non-structural polypeptide. Evidence is presented that viral polypeptide F₀ (mol wt 66,000), which was found in each cell type, may be the precursor of viral proteins F₁ (mol wt 52,000) and F₂ (mol wt < 20,000). (39 refs.)

77-7010 Temperature-sensitive Variants for Saturation Density and Anchorage Dependency of a Simian Virus 40-transformed Human x Mouse Hybrid Cell Line. (Eng) Rovera, G. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA 19104); Hyland, J.; Ming, P. M. *J Natl Cancer Inst* 58(3): 711-716; 1977.

Several variant clones temperature-sensitive (ts) for some parameters of transformation were isolated from a hybrid cell line containing a stable diploid mouse genome and two human chromosomes 7 carrying an integrated defective simian virus 40. Like wild-type (wt) cells, the ts clones grew to high saturation densities and readily formed colonies in methylcellulose at the permissive temperature. In contrast to wt cells, at the nonpermissive temperature they had variable but always lower saturation densities and were unable to form colonies in methylcellulose. The fraction of cells that synthesized DNA decreased at both temperatures when the cells reached saturation density, but it always represented at least 20% of the total population. All of the ts clones tested had a near

triploid chromosome number, contained from one to three human chromosomes 7, and were T-antigen-positive both at the permissive and nonpermissive temperatures. The ts clones maintained a low saturation density at the nonpermissive temperature because of a decrease in actively proliferating cells and because of the shedding of cells into the medium. Temperature downshifts and refeeding allowed for expression of the permissive phenotype. In most of the isolated clones, anchorage independency was not correlated with unrestricted cell proliferation. These variant clones may be useful in studies of the interdependent pathways involved in the expression of the phenotype of a transformed cell and the molecular mechanism required for the maintenance of a normal state in a cell population. (21 refs.)

- 77-7011 Assignment of the Integration Site for Simian Virus 40 to Chromosome 17 in GM54VA, a Human Cell Line Transformed by Simian Virus 40.** (Eng) Croce, C. M. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA 19104). *Proc Natl Acad Sci USA* 74(1): 315-318; 1977.

GM54VA human cells transformed by simian virus 40 (SV40) were hybridized to peritoneal macrophages (MPM) from three mouse strains and to thymidine kinase-deficient mouse and Chinese hamster cells. The hybrids were studied for the expression of SV40 tumor antigen (T antigen) and for the presence of human chromosomes. All 27 hybrid clones derived from the fusion of C57BL, BALB/c, and B6-GIX + MPM with GM54VA cells were positive for SV40 T antigen in 100% of their cells and contained human chromosome 17. This chromosome was the only human chromosome present in five of the hybrid clones. Fusion of GM54VA cells and the thymidine kinase-deficient mouse or hamster fibroblasts resulted in the growth in hypoxanthine-aminopterin-thymidine medium of hybrid SV40 T-antigen-positive and -negative clones. Counterselection of the T-antigen-positive hybrid clones in 5-bromodeoxyuridine-containing medium resulted in the growth of T-antigen-negative hybrid cells and in the loss of human chromosome 17, confirming the fact that the SV40 genome is integrated in human chromosome 17 in SV40-transformed GM54VA cells. Since three clones were SV40 T-antigen-negative but also contained human chromosome 17, it is concluded that the SV40 genome is integrated in only one of the two human chromosomes 17. The genome of SV40 was assigned to human chromosome 7 in two other SV40-transformed human cell lines studied previously. These results indicate that at least two different integration sites for SV40 are present in human cells: one located in human chromosome 7 and the other in human chromosome 17. (21 refs.)

- 77-7012 Separation of Cells Containing R-Type Virus-like Particles from a Simian Virus 40-induced Hamster Tumor Cell Line.** (Eng) Bergman, D. G. (Dept. Microbiology, Ohio State Univ., Coll. Biological Sciences, Columbus, OH 43210); Blakeslee, J. R.; Wolff, D. A. *J Natl Cancer Inst* 58(2): 295-299; 1977.

Cells from a simian virus 40 (SV40)-induced Syrian hamster fibrosarcoma (SV40HT) were separated into two distinct fractions using colloidal silica density-gradient centrifugation. The lighter cell fraction (F1) had a buoyant density of 1.054-1.074 g/ml and comprised 95.3% of the total cells. Both cell fractions were tumorigenic and did not differ greatly in cell type, viability, mitotic index, or their ability to incorporate ³H-thymidine. Ultrastructurally, the F1 cells contained R-type viruslike particles within dilated intracisternal spaces and exhibited cytoplasmic vacuoles. This vacuolization may be responsible for their lighter buoyancy. The F2 cells had little or no vacuolization of the cytoplasm and seldom harbored R-type viruslike particles. The F2 cells demonstrated a twofold greater ability to incorporate ¹⁴C-protein hydrolysate into proteins than the F1 cells. The results suggest that synthesis of R-type viruslike particles at the membranes of the rough endoplasmic reticulum may alter the protein-synthesizing capabilities of cells. (13 refs.)

- 77-7013 Characterization of Simian Virus 40-transformed African Green Monkey Cells (CV-1). II. Semipermissive Character for Viral Replication.** (Eng) Kashmiri, S. V. (Dept. Pharmacology, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD); Hirai, K. *Microbiol Immunol* 21(8): 475-479; 1977.

The rescue of infectious simian virus 40 (SV40) from a T-antigen-positive but V-antigen-negative clone (C1-15a) of transformed African green monkey kidney cells was attempted by Sendai virus-mediated cell fusion. Heterokaryons formed by fusion of C1-15A cells with cells resistant or susceptible to SV40 superinfection did not induce SV40 T and V antigens or cytopathic effects in monolayers of SV40-transformed monkey kidney cells. These results were not solely due to the defectiveness of the integrated viral genome in C1-15a, since fusion of the cells with SV40-transformed mouse cells released infectious SV40 particles with very low efficiency. It is concluded that most C1-15a cells have inadequate levels of the cytoplasmic factors required for SV40 replication. (9 refs.)

- 77-7014 Histone Synthesis During Infection of Monkey Kidney Cells with Simian Virus 40.** (Eng) Kay, A. C. (Lab. Biochemistry, NCI, NIH, Bethesda, MD 20014); Singer, M. F. *Nucleic Acids Res* 4(10): 3371-3386; 1977.

Synthesis of viral and cellular DNA and histones was investigated in BSC-1 monkey kidney cells infected with 10 to 40 plaque-forming units per cell of simian virus 40 (SV40) strain 777. Early after infection, viral DNA synthesis followed a time course similar to that observed for cellular DNA synthesis. Viral DNA replication was first detected at 17 hr; it was well underway by 21 hr and substantially increased by 34 hr. At later times, viral DNA synthesis continued but cellular DNA synthesis declined. By 72 hr, viral DNA synthesis constituted the bulk of DNA synthesis. Synthesis of all classes of histones greatly increased by 21 hr after infection and con-

continued to increase at 34 hr. By 48 hr, however, it had decreased and at 72 hr, it was less than that in controls, in spite of the high level of viral DNA synthesis. This low level was not the result of a massive degradation of cellular histones. Thus, the rates of histone synthesis do not have a tight temporal relationship to the rates of SV40 DNA synthesis. Histone synthesis was detectable as early as 11 hr after infection; thus, the early increase in synthesis could be the result of the SV40 infection itself rather than of the accompanying stimulation of cellular DNA synthesis. H1 synthesis increased relative to that of the other histones, but it was synthesized at about half the rate. (28 refs.)

77-7015 Changes in Leucine Aminotransferase Isozymes by Viral Transformation and Its Correlation with the Isozyme Changes Occurring During Differentiation. (Eng) Roth, S. L. (Dept. Microbiology, Sch. Medicine, Univ. Pennsylvania, Philadelphia, PA 19174); Delotto, R.; Kaji, A. *Cancer Res* 37(4): 1147-1153; 1977.

The leucine aminotransferase isozyme pattern was investigated in various cell lines and their virus-transformed derivatives. Wistar 3C rat liver cells contained only isozyme I, but their simian virus 40-transformed counterparts had isozyme II in addition to isozyme I. In addition, a spontaneously transformed late-passage clone of these cells acquired isozyme III. Polyoma virus-transformed baby hamster kidney cells also exhibited a greater predominance of isozyme III than their normal untransformed counterparts. Examination of the isozyme in cloned normal rat kidney cells transformed by a temperature-sensitive mutant of Rous sarcoma virus indicated that isozyme change correlates with transformation. When grown at 36°C, these cells contained predominantly isozyme III; however, upon reacquiring normal morphology and lowered glucose transport activity when grown at 40°C, isozyme I predominated, similar to normal adult rat kidney tissue. Isozyme III was present in neonatal rat and hamster kidney tissue, and its predominance in the virus-transformed rat and baby hamster kidney cells was interpreted as indicative of the dedifferentiation in these cells upon viral transformation. A similar change in isozyme patterns was observed in developing chicken embryos: form III was predominant in 5-day-old embryos, but form I was predominant in the more-differentiated day 17-embryos. (37 refs.)

77-7016 Overlapping of the VP₂-VP₃ Gene and the VP₁ Gene in the SV40 Genome. (Eng.) Contreras, R. (Lab. Molecular Biology, State Univ. Ghent, Ledeganckstraat, 35, B-9000 Ghent, Belgium); Rogiers, R.; Van de Voorde, A.; Fiers, W. *Cell* 12(2): 529-538; 1977.

The nucleotide sequence of the simian virus 40 Hind E fragment was determined. The sequence of the strand with the same polarity as late messenger RNA has a unique reading frame. It continues in Hind K and terminates with a UAA signal located 110 nucleotides inside the major structural pro-

tein, VP₁, gene. The amino acid sequence that is derived from the nucleotide sequence covers a major part of the VP₁ protein. A hairpin structure, which contains the VP₁ gene initiation signal, may function as a recognition signal for processing enzymes or as a negative control for expression of the VP₁ gene. (41 refs.)

77-7017 Nucleotide Sequence of a Fragment of SV40 DNA That Contains the Origin of DNA Replication and Specifies the 5' Ends of 'Early' and 'Late' Viral RNA. IV. Localization of the SV40 DNA Complementary to the 5' Ends of Viral mRNA. (Eng) Dhar, R. (Dept. Human Genetics, Yale Univ. Sch. Medicine, New Haven, CT 06510); Subramanian, K. N.; Pan, J.; Weissman, S. M. *J Biol Chem* 252(1): 368-376; 1977.

Cytoplasmic (messenger RNA) isolated from cells infected with (simian virus 40) was isolated by passage over oligo(dT)-cellulose columns. This RNA was annealed to SV 40 DNA fragments produced by cleavage with EcoRII endonuclease. The RNA resistant to RNase digestion was analyzed by digestion with ribonucleases and oligonucleotide mapping. The results were compared with oligonucleotides from in vitro transcripts of the fragments and with whole-genome SV 40 complementary RNA that had been fractionated by hybridization to the fragments. The 5' ends of early and the large late SV40 mRNA, transcribed from opposite DNA strands, overlap for a region of 60-100 nucleotides. This region includes a portion of the DNA segment containing the origin of DNA replication. (44 refs.)

77-7018 RNA Primers in SV40 DNA Replication: Identification of Transient RNA-DNA Covalent Linkages in Replicating DNA. (Eng) Anderson, S. (Dept. Biological Chemistry, Harvard Medical Sch., Boston, MA 02115); Kaufmann, G.; DePamphilis, M. L. *Biochemistry* 16(23): 4990-4998; 1977.

RNA-DNA covalent linkages in replicating simian virus 40 (SV40) DNA were quantitated by measuring the release of 2' (3')-³²P-ribosomal nucleoside monophosphates (rNMP's) from alkali-treated ³²P-DNA. More than 96% of the released label was in the 2' (3')-³²P-rNMP's, as shown by chemical conversion of individual labeled nucleotides to cyclic nucleotides, followed by enzymatic cleavage of the latter to produce 3' ³²P-rNMP's. α-³²P-deoxyribonucleoside triphosphate (dNTP), incorporated into DNA, was identified as the ³²P donor because the amount of ³²P label transferred was proportional to the specific radioactivity of the labeled substrate. All 16 possible rN-dN linkages were found in SV40-replicating DNA at frequencies that suggested a near-random distribution on the genome. These RNA-DNA covalent linkages behaved as transient intermediates in DNA synthesis; they disappeared at the same rate that nascent 4S DNA chains (Okazaki pieces) were joined to the growing daughter strands. Therefore, these linkages exhibited kinetic properties consistent with the proposed role of RNA as a primer for

discontinuous DNA synthesis. When 4S DNA joining was inhibited by the absence of cytosol, the disappearance of RNA-DNA covalent linkages was not prevented. Inhibition of DNA synthesis with either cytosine 1- β -D-arabinoside-5'-triphosphate or adenine-9- β -D-arabinoside-5'-triphosphate also failed to block the removal of RNA-DNA covalent linkages. Thus, excision of these putative RNA primers does not appear to require the concomitant joining of 4S DNA chains or DNA synthesis. (32 refs.)

- 77-7019 **The Chromosome Analysis and Susceptibility to Transformation by Simian Virus 40 of Fibroblasts from Ataxia-Telangiectasia.** (Eng) Webb, T. (Dept. Cancer Studies, Univ. Birmingham, Medical Sch., Birmingham B15 2TJ, England); Harnden, D. G.; Harding, M. *Cancer Res* 37(4): 907-1002; 1977.

Chromosome analyses were performed for 14 lines of fibroblasts from 8 ataxia telangiectasia (ATT) patients and 14 lines from 10 control patients. Compared with control cells, ATT cells had an elevated incidence of chromosome damage, including gaps and breaks, rings, dicentric and fragments, and chromosome figures. The similar abnormalities in cell lines from different ATT patients suggested a degree of specificity for chromosome involvement in rearrangements. D- and B-group aberrations, which resulted in Dq+ and Bq+, were frequent, and breakage of chromosome 1 at the centromere was detected in 6/12 ATT lines. The simian virus 40 transformation rates for ATT cells were within the normal range. There was no direct correlation between the transformation rate of a particular cell line and its degree of chromosome damage. (29 refs.)

- 77-7020 **Recombination Between Endogenous and Exogenous Simian Virus 40 Genes. I. Rescue of a Simian Virus 40 Temperature-sensitive Mutant by Passage in Permissive Transformed Monkey Lines.** (Eng) Gluzman, Y. (Dept. Virology, Weizmann Inst. Science, Rehovot, Israel); Kuff, E. L.; Winocour, E. *J Virol* 24(2): 534-540; 1977.

An attempt was made to rescue the simian virus (SV40) temperature-sensitive (*ts*) mutant *tsD202* at the permissive temperature in three permissive lines of SV40-transformed monkey CV1 cells. The permissive lines, C2, C6, C11, were initially transformed by SV40 strain 777. Passage on *tsD202* cells led to a 10³- to 10⁶-fold increase of *ts* virus compared to normal passage on CV1 cells. The proportion of the rescued virus in the yield increased dramatically between passages 1 and 2 on the transformed cells. It is assumed that the proportion of rescued virus is amplified during passage 2 because it grows faster than the nonrescued fraction of the *ts* population. Similar experiments with *tsA30* and *tsA209* resulted in the production of only small amounts of temperature-insensitive virus. The rescued virus passaged on C11 cells at 33.5 C produced a typical single-hit, dose-response curve when plated at 40.5 C on normal CV1 cells. Experi-

ments with *tsB204* and *tsC219* cells also failed to rescue virus because they, like C2, C6, and C11, are already late mutant of SV40. The *tsA30* and *tsA209* mutants were not rescued probably because of the nature of the resident SV40 genome in the transformed cells. (12 refs.)

- 77-7021 **Recombination Between Endogenous and Exogenous Simian Virus 40 Genes. II. Biochemical Evidence for Genetic Exchange.** (Eng) Vogel, T. (Dept. Virology, Weizmann Inst. Science, Rehovot, Israel); Gluzman, Y.; Winocour, E. *J Virol* 24(2): 541-550; 1977.

The genome of the simian virus 40 (SV40) temperature-sensitive (*ts*) mutant *tsD202*, rescued by passage on C2, C6, or C11 permissive monkey cell lines, was analyzed by restriction endonuclease cleavage mapping. The endonuclease R. *Hae*III cleavage site was missing on the parenteral *tsD202* DNA and three independent revertants of the virus, but it was present in 4/5 independently rescued *D202* populations and in the DNA of SV40 strain 777, which was used to transform the cells. Comparison of the endonuclease R. *Hin*II + III cleavage patterns of SV40 777 DNA and *tsD202* DNA revealed differences in the electrophoretic mobilities of *Hin* fragments A, B, and F. However, the corresponding fragments from the rescued genomes were identical to those of *tsD202* DNA. These results indicate that the rescued *D202* viruses are true recombinants, with cleavage sites characteristic of both parents, the endogenous SV40 genome of transformed cells, and the exogenous mutant. Studies to date do not permit the definition of precise boundaries of the segments exchanged in the recombinant populations. Recombination between endogenous integrated genomes and exogenous viruses may account for the heterogeneity of properties of RNA tumor viruses. (22 refs.)

- 77-7022 **Regulation of DNA Chain Elongation in SV3T3 Cells in Relation to Growth Rate.** (Eng) Venkatesan, N. (Childrens Hosp. Los Angeles, Div. Hematology Oncology, Los Angeles, CA 90027). *Biochim Biophys Acta* 478(4): 454-460; 1977.

The regulation of DNA synthesis was investigated in simian virus 40-transformed 3T3 (SV3T3) cells exhibiting variable growth rates and residence times in S phase when cultured in the presence of different serum concentrations. Pulse-labeled DNA was chased into large mol wt material in vivo much more slowly in slowly growing cells than in cells growing at the normal rate. Moreover, the joining of short (< 10 S) chains to form long (> 10 S) chains by a whole cell lysate system in vitro was greatly impaired in slowly growing cells compared to controls. Thus the lengthening of the S phase in SV3T3 cells growing slowly in low serum was reflected in a reduced rate of DNA chain elongation. The presence of cycloheximide during chase in vivo reduced the conversion rate of pulse-labeled molecules into large mol wt DNA in both slowly and normally growing cells. (12 refs.)

77-7023 Protein Synthesis in 3T3 and SV40-transformed 3T3 Cells. Activity of Ribosomes and Cytosol Proteins in Cell-free Protein Synthesis. (Eng) Conta, B. S. (Dept. Microbiology, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY 14642); Meisler, A. I. *J Biol Chem* 52(21): 7640-7647; 1977.

The activity of specific components involved in protein synthesis in 3T3 cells and their simian virus 40 (SV40)-transformed derivatives, SV3T3, was examined in a cell-free protein synthetic system. The results correlated with previous studies indicating that a decreasing rate of protein synthesis does not accompany the stationary phase of growth. The 3T3 and SV3T3 polysome preparations containing endogenous messenger RNA were equally efficient in supporting cell-free protein synthesis in this system. Net protein synthesis was not altered by an increase in the population density of the cellular polysome source. The activity of the aminoacyl-transfer RNA synthetase enzymes from 3T3 and SV3T3 cells was examined in vitro after isolation by pH 5 precipitation and by ammonium sulfate fractionation. The activity of these preparations from stationary phase 3T3 and nonexponential phase SV3T3 cells was approx three times higher than the activity of fractions from the homologous exponential phase cell. However, at both growth stages, the SV3T3 preparations were 30-40 times more active than the 3T3 preparations. These findings may have implications for the different growth properties observed in the two cell types. (16 refs.)

77-7024 Identification of Simian Virus 40 Protein A. (Eng) Rundell, K. (Dept. Microbiology/Immunology, Northwestern Univ.-McGaw Medical Center, Chicago, IL 60611); Collins, J. K.; Tegtmeier, P.; Ozer, H. L.; Lai, C. J.; Nathans, D. *J Virol* 21(2): 636-646; 1977.

Simian virus 40 (SV40) protein A, suspected of being either the tumor (T) antigen or a protein associated with T antigen, was studied by immunoprecipitation techniques using the TC7 clone of CV-1 cells. This protein can be immunoprecipitated with antiserum from hamsters with SV40-induced tumors. The protein migrates at a position corresponding to either 88,000 or 100,000 daltons on two different electrophoresis systems. Cell lines infected with two different strains of SV40 synthesize immunoreactive proteins that differ slightly in mobility during sodium dodecylsulfide-polyacrylamide gel electrophoresis, evidence that the protein is coded for by the virus. The differences in protein size correlate with differences in the electrophoretic mobility of viral DNA fragments obtained by digestion with *Hind*II and III restriction enzymes. The size of the viral capsid proteins VP2 and VP3 also varies with the strain of virus. Purification and reaction with anti-T serum indicated that the protein is the T antigen. A 33,000-dalton polypeptide fragment produced by *d*-1001 cells corresponded to maps of tryptic peptides from the 88,000- to 100,000-dalton protein, providing evidence that all three are products of the SV40 *A* gene. The deletion fragment reacts with anti-T sera and binds to double-stranded DNA in the presence of the complete A protein. (37 refs.)

77-7025 Mapping of Sequences with 2-fold Symmetry on the Simian Virus 40 Genome: A Photochemical Crosslinking Approach. (Eng) Shen, C. K. (Dept. Chemistry, Univ. California, Berkeley, CA 94720); Hearst, J. E. *Proc Natl Acad Sci USA* 74(4): 1363-1367; 1977.

Sequences with twofold axes of symmetry were detected and mapped on the simian virus 40 (SV40) genome by their ability to form hairpin turns in single-stranded SV40 DNA. Supercoiled SV40 DNA (SV40 I) was digested with restriction enzymes *Eco*RI and *Hpa*II. The resulting linear DNA molecules, with lengths of the complete SV40 genome, were then denatured and photochemically reacted with 4,5',8-trimethylpsoralen (trioxsalen) at 16.0 C and different ionic strengths. Secondary structures on the single-stranded SV40 DNA were crosslinked and their positions analyzed by electron microscopy. No hairpin turns were observed on denatured SV40 DNA photoreacted in 1 millim Tris HCl/0.1 millim EDTA at pH 7.0. In 20 millim NaCl, one specific hairpin turn was detected at 0.17 map unit on the map of *Eco*RI-digested SV40 DNA, where the 3' ends of early 19S messenger RNA (mRNA), late 19S mRNA, and 16S mRNA of SV40 have been mapped. In 30 millim NaCl, five additional major hairpin turns were observed. The centers of four of these specific hairpin turns were mapped at 0.26, 0.68, 0.84, and 0.94 unit on the map of *Eco*RI digested SV40. The fifth is at or near the unique *Eco*RI cleavage site on SV40 DNA. The possible functions of these sequences are discussed in terms of the nature of promoter sites, replication origin, processing of RNA precursors, and regulation at the translational level. (39 refs.)

77-7026 Biological and Biochemical Studies of Cells Transformed by Simian Virus 40 Temperature-sensitive Gene A Mutants and A Mutant Revertants. (Eng) Tenen, D. G. (Div. Medical Oncology, Sidney Farber Cancer Inst., Boston, MA 02115); Martin, R. G.; Anderson, J.; Livingston, D. M. *J Virol* 22(1): 210-218; 1977.

The growth properties of hamster cells transformed by wild-type simian virus 40 (SV40), by early SV40 temperature-sensitive (*ts*) mutants of the *A* complementation group, and by spontaneous revertants of these mutants were studied. All but one of the *tsA* mutant-transformed cell lines were *ts* in their ability to form clones in soft agar and on monolayers of normal cells; CHLA-30L1 cells were not *ts* in the latter property. All cells transformed by stable revertants of well-characterized *tsA* mutants possessed certain growth properties in common with wild-type-transformed cells at both temperatures. Virus rescued from *tsA* transformants, including CHLA30L1, was *ts* for viral DNA replication, but that rescued from revertant and wild-type transformants was not thermolabile in this function. T antigen present in crude extracts of *tsA*-transformed cells, including CHLA30L1, grown at 33 or 44 C, was *ts* by in vitro immunoassay, but that from wild-type-transformed cells was relatively stable. T antigen from revertant transformants was more stable than the *tsA* protein. Partially

purified T antigen from revertant-transformed cells was nearly as stable as wild-type antigen in its ability to bind DNA after heating at 44 C, whereas T antigen from *tsA30* mutant-transformed cells was relatively thermolabile. These results indicate that T antigen is a product of the SV40 A gene. Significantly more T antigen was found in extracts of CHLA30L1 grown in high density at the nonpermissive temperature than in any other *tsA*-transformed cell similarly grown. This is consistent with the suggestion that the amount of T antigen synthesized in CHLA30L1 is large enough to allow partial expression of the transformed phenotype at the restrictive temperature. Alternatively, the increase in T-antigen concentration may be secondary to one or more genetic alterations that independently affect the transformed phenotype of these cells. (37 refs.)

- 77-7027 **Modification of Simian Virus 40 Protein A.** (Eng) Tegtmeier, P. (Dept. Microbiology, State Univ. New York, Stony Brook, NY 11794); Rundell, K.; Collins, J. K. *J Virol* 21(2): 647-657; 1977.

The phosphorylation of Simian virus 40 protein A during productive and transforming infections was studied in CV-1 and BSC-1 cells. Infection by A mutants and wild-type virus results in equal amounts of phosphorylated protein, indicating that the functional defect in the mutants is not related to phosphorylation. Extracts of cells infected by wild-type virus contained three forms of the A protein, with mol wts corresponding to 85,000, 88,000, and 100,000 daltons. Following exposure to Nonidet P-40 the 85,000- and 88,000-dalton proteins were found in extracts of permissive cells, but not in extracts of transformed cells. This finding raised the question of the functional importance of the smaller proteins in productive infection. However, the absence of the smaller proteins in some extracts of the fully permissive cell line CV-1 indicates that conversion of the A protein from the larger to the smaller forms is not required in significant amounts for productive infection. It is suggested that a cytoplasmic factor is involved in conversion of the 100,000-dalton protein to the 85,000-dalton protein during extraction. (27 refs.)

- 77-7028 **Assembly of SV40 Chromatin in a Cell-free System from *Xenopus* Eggs.** (Eng) Laskey, R. A. (Medical Res. Council, Lab. Molecular Biology, Hills Road, Cambridge, CB2 2QH, England); Mills, A. D.; Morris, N. R. *Cell* 10(2): 237-243; 1977.

A cell-free system is described that assembles chromatin from purified DNA in 1 hr under physiological incubation conditions. It consists of a 145,000 x g (max) supernatant fraction from eggs of *Xenopus laevis*. It converts simian virus 40 (SV40) DNA to a nucleoprotein that cosediments with naturally occurring SV40 chromatin and that can be cleaved by micrococcal nuclease to a highly ordered pattern of DNA fragments resembling those resulting from the digestion of liver chromatin. The system inserts superhelical turns into relaxed, covalently closed DNA. The assembly process is not

cooperative since under limiting conditions, each DNA molecule becomes partially assembled. Assembly does not require DNA replication or protein synthesis, but it occurs from a stored histone pool of at least 40 nanograms/egg. Under conditions of DNA excess, assembly becomes dependent on the amount of exogenous histones. Apart from histones and a nicking-closing activity, chromatin assembly requires an additional thermolabile factor present in the egg supernatant. (35 refs.)

- 77-7029 **Compact Form of SV40 Viral Minichromosome is Resistant to Nuclease: Possible Implications for Chromatin Structure.** (Eng) Varshavsky, A. J. (Genetics Unit, Massachusetts General Hosp., Boston, MA 02114); Nedospasov, S. A.; Schmatchenko, V. V.; Bakayev, V. V.; Chumackov, P. M.; Georgiev, G. P. *Nucleic Acids Res* 4(10): 3303-3325; 1977.

The histone H1-containing simian virus 40 (SV40) minichromosomes extracted from the nuclei of lytically infected cells were investigated. Under physiological salt conditions the sedimentation coefficient of the minichromosomes was 80S to 85S with SV40 DNA I as a sedimentation marker and 70S to 75S with mouse 60S ribosomal unit as a sedimentation marker. The minichromosomes existed in a more compact conformation than at low ionic strength (IS). They sedimented at 80S to 85S at high IS and 37S at low IS. Electron microscopy of H1-depleted minichromosomes revealed typical circular headed structures in both high- and low-IS buffers; however, at high IS the H1-containing minichromosomes were much more compact than at low IS. Metal shading of the minichromosomes revealed roughly spherical particles 350 to 400 Å in diameter; this value changed to 250 to 300 Å upon staining. The minichromosomes extracted from cells at 40 to 42 hr after lytic infection lacked significant amounts of virus-specific capsid antigen. Thus, their compact configuration is entirely due to interactions between covalently closed DNA and five eukaryotic histones. The minichromosomes were resistant to staphylococcal nuclease, even after storage at low temperatures. It is suggested that the nuclease-sensitive parts of the linker regions are not exposed on the surface of compact chromosomes. On the other hand, pancreatic DNase readily attacks these minichromosomes. (47 refs.)

See also:

- *(Rev.): 77-6629, 77-6638, 77-6639, 77-6640, 77-6641, 77-6642, 77-6643, 77-6644, 77-6645, 77-6646, 77-6652.
*(Chem.): 77-6858.
*(Phys.): 77-6908.
*(Immun.): 77-7042, 77-7043, 77-7052, 77-7053, 77-7054, 77-7055, 77-7056, 77-7057, 77-7065, 77-7066, 77-7070, 77-7081, 77-7082, 77-7085, 77-7088, 77-7089, 77-7090, 77-7091.
*(Path.): 77-7094, 77-7121, 77-7139, 77-7141.
*(Epid.-Biom.): 77-7155, 77-7160.

IMMUNOLOGY

7-7030 **Immunosubversive Activity of Tumor Cells as an Escape Mechanism.** (Eng) Plescia, O. J. Waksman st. Microbiology, Rutgers, State Univ. New Jersey, New Brunswick, NJ 08903; Grinwich, K.; Smith, A.; Sheridan, J.; Plescia, A. M. In: *Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York: Academic Press, Inc.): 825 pp.; 288-310; 1977.

Research designed to probe the subversive nature of tumor cells in normal, immunologically functional, histocompatible hosts is reviewed. Inbred strains of mice bearing syngeneic tumors of viral or chemical etiology were challenged with (1) sheep RBC to study antibody response, (2) tumor allografts to study cellular response, (3) T-cell and B-cell mitogens to identify the target of subversiveness, and (4) viable *Torulopsis labrata*, a microorganism that is normally killed by mononuclear phagocytes, to assess the integrity of the mononuclear phagocytic system. Generalized immunodepression occurred in association with tumor growth and strongly antigenic tumor allografts suppressed both cellular and antibody responses. Spleen cells from tumor bearers showed a progressive loss of response to the T-cell mitogen, phytohemagglutinin, but no significant change in response to the B-cell mitogen, lipopolysaccharide. Phagocytic cells were not depressed by the action of the syngeneic tumors. Certain prostaglandins may be mediators of T-cell suppression by tumor cells; the possible role of cyclic AMP as a messenger of this activity is discussed. (38 refs.)

7-7031 **Lysis of Human Normal and Sarcoma Cells in Tissue Culture by Normal Human Serum: Implications for Experiments in Human Tumor Immunology.** (Eng) Rosenberg, S. A. (Surgery Branch, NCI, NIH, Public Health Service, U.S. Dept. Health, Education, and Welfare, Bethesda, MD 20014). *J Natl Cancer Inst* 58(5): 1233-1238; 1977.

Sera from 8/9 osteogenic sarcoma patients lysed autologous tissue-cultured cells of both skin and osteosarcoma equally in the presence of complement. Of 155 normal human sera tested, 103 lysed allogeneic normal skin in tissue culture. These antibodies were more prevalent in younger (96% in ages 11-20 yr) than older (33% in ages 41-50 yr) subjects. The presence of these natural antibodies against normal and malignant cells growing in tissue culture was possibly directed against components adsorbed to the cells during tissue culture or to new cell-surface antigens expressed by these cells

in tissue culture. These non-tumor-related neoantigens on normal and malignant cells in tissue culture represent a potential source of confusion in studies of the serologic response of humans to tumors. (18 refs.)

77-7032 **Immunodeficiency in Patients with Non-Hodgkin Lymphomas.** (Eng) Jones, S. E. (Section Hematology and Oncology, Dept. Medicine, Univ. Arizona Coll. Medicine, 1501 N. Campbell Ave., Tucson, AZ 85724); Griffith, K.; Dombrowski, P.; Gaines, J. A. *Blood* 49(3): 335-344; 1977.

Seventy-one untreated patients with non-Hodgkin lymphomas were studied for number of peripheral blood lymphocytes, serum immunoglobulins, and delayed hypersensitivity to six recall antigens. The results were correlated to histology (Rappaport classification), stage (Ann Arbor classification), presence of symptoms, and survival. As a group, 38 patients with diffuse lymphomas exhibited marked impairment in reactivity to five of six antigens. Lymphopenia and reduced serum IgA levels were found in association with diffuse histiocytic lymphoma. Lymphocyte number and skin test reactivity tended to be greater in diffuse lymphoma patients with localized disease or without constitutional symptoms: survival was superior for patients free of symptoms. As a group, 33 patients with nodular lymphoma had normal numbers of lymphocytes, lower serum IgG and IgA levels and significant impairment of reactivity to two antigens (streptokinase-streptodornase and mumps). Their reactivity to three other antigens (*Candida albicans*, coccidioidin, and tuberculin) was normal. Survival for patients with nodular lymphoma was superior compared to those with diffuse lymphomas. The results indicate a severe immunodeficiency in patients with diffuse lymphoma (particularly diffuse histiocytic lymphoma) and a definite, but much less severe, immunodeficiency in patients with nodular lymphoma. (30 refs.)

77-7033 **Suppression of Antibody-mediated and Cell-mediated Murine Immunity by the Carcinogen N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide.** (Eng) Headley, D. B. (Dept. Human Oncology, Univ. Wisconsin Center Health Sciences, 1300 University Ave., Madison, WI 53706); Cohen, S. M.; Bryan, G. T. *Cancer Res* 37(4): 974-979; 1977.

N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide (NFTA), administered at 1,000 ppm in the diet of female BALB/c mice for 12 wk, induced a high incidence of lymphocytic leukemia. The effects of NFTA on antibody and cell-mediated immunity were studied using the spleen plaque assay for detection of IgM-producing cells and the graft-vs-host (GVH) reaction, respectively. NFTA suppressed both responses. In mice given 1,000 ppm for 6 days, the number of antibody-forming cells (AFC) to sheep RBC was significantly less than that in control mice. The GVH reaction was not suppressed at 21 days, but was severely suppressed at 70 days, prior to the histological appearance of leukemia. Dose-response studies showed a significant suppression of the number of AFC/spleen with 250, 500, and 1,000 ppm NFTA, but not with 100 ppm. The degree of suppression was greatest at 250 ppm. Suppression of cell-mediated immunity by NFTA was directly proportion to dose. Suppression of antibody-mediated immunity in relation to the induction of leukemia at 28 wk was studied by feeding NFTA at 500 ppm for 14 wk, followed by unmedicated diet for 14 wk. During the 11th week, mice were immunized with sheep RBC; 5 days later the spleens were removed and the spleen plaque assay was performed. Eight of 18 mice fed NFTA developed leukemia. The number of AFC/spleen in leukemic (78×10^3) and nonleukemic (68×10^3) mice was significantly lower than the number in controls (170×10^3). A closely related carcinogenic nitrofurantoin, 4N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide, did not suppress the antibody-mediated immune response measured during the 11th week of administration. (37 refs.)

77-7034 A Time Factor in the Success or Failure of Immune Rejection of Transplanted Tumors. (Eng)

Vaage, J. (Dept. Cancer Therapy Development, Pondville Hosp., Walpole, MA 02081). *Cancer Res* 37(4): 1064-1067; 1977.

Changes in susceptibility to immune rejection were studied and compared during the initial stages of sc and pulmonary establishment of a transplanted syngeneic C3H mouse mammary carcinoma. The time of immunological attack on the implanted tumor cells was varied by two procedures. In one experiment, mice immunologically suppressed by the presence of large sc tumor implant were surgically cured before sc challenge. However, the immune recovery that normally follows tumor removal was delayed for increasing lengths of time after challenge by injections of irradiated tumor cells. In another experiment, mice were immunologically impaired by sublethal whole-body irradiation before sc and iv challenge. Immune rejection reactivity was then introduced by passive transfers of lymph node cells from immunized mice, at increasing intervals after the challenge implantations of tumor cells. In both experiments, the number of tumor takes increased if tumor immunity was reduced or absent for at least 3 days after challenge. If tumor immunity was restored

or provided by the third day after challenge, the number of observed tumors decreased abruptly. The reduction in the effectiveness of immunosupportive treatments about the third day after tumor implantation may indicate a reduction in vulnerability to immune rejection that coincides with vascularization of the implants. (16 refs.)

77-7035 Immunosuppression Studies in Foreign Body Tumorigenesis: No Evidence for Tumor-specific Antigenicity. (Eng) Michelich, V. J. (Dept. Microbiology,

Medical Sch., Univ. Minnesota, Minneapolis, MN 55455); Buoen, L. C.; Brand, K. G. *J Natl Cancer Inst* 58(3): 757-761; 1977.

The effect of immunosuppression on the frequency and latency of foreign body (FB)-induced sarcomas and the antigenicity of these tumors were investigated. Sarcomas were induced in CBA/H strain mice by sc implantation of polyvinyl chloride vinyl acetate copolymer films. The mice had been immunosuppressed by azathioprine (4 mg/kg/day beginning 1 wk before implantation and continuing throughout the experiment), antilymphocyte globulin (0.25 ml of a 1:4 dilution ip on days 0, 1, 4, and 6 before tumor challenge and weekly thereafter), or thymectomy 48 hr after birth. Compared to nonimmunosuppressed controls, all three treatments did not affect the appearance of FB-induced sarcomas. No tumor-specific transplantation antigens could be demonstrated in the sarcomas of immunosuppressed mice. On the basis of these results, the concept of immune surveillance as a natural host defense mechanism against carcinogenesis does not apply to this model of tumor development. (36 refs.)

77-7036 Immunobiology of Heterotransplanted Human Tumors in Nude Mice. (Eng) Gershwin, M. E.

(Section Rheumatology-Clinical Immunology, Dept. Internal Medicine, Sch. Medicine, Univ. California, Davis, CA 95616); Ikeda, R. M.; Kawakami, T. G.; Owens, R. B. *J Natl Cancer Inst* 58(5): 1455-1461; 1977.

The immunobiology of heterotransplanted human tumors was investigated following their transplantation into nude mice. The tumors included bronchogenic, colonic, rectal, ovarian, gastric, endometrial, vaginal, bladder, renal, esophageal, embryonic cell, pancreatic, and breast carcinoma, as well as fibrosarcoma, rhabdomyosarcoma, malignant melanoma, astrocytoma, Wilms' tumor, endometrial hyperplasia, and hydatidiform mole. Several of the tumors were passaged up to 15 generations. During these passages no changes were noted in latency period for tumor development or in histology. Several tumors differed significantly in the minimum number of cells required for successful transplantation; the differences were independent of the basic biologic aggressiveness of the individual tumors. Nude mice that received fibrosarcoma and endometrial carcinoma transplants

had increased serum IgM, spleen cell numbers, and complement receptor lymphocytes. These changes were not seen in mice that received malignant melanoma transplants. In contrast, there were no apparent differences in the responses of nude mice given transplants to the T-cell mitogens concanavalin A or phytohemagglutinin or in the number of θ -bearing spleen cells. The success rate for transplantation improved significantly when explants rather than single-cell suspensions were used. Tumors transplanted to nude mice derived from strictly homozygous matings behaved like tumors transplanted to mice born of heterozygous mothers. Despite the dramatic size of sc tumor nodules, there were no examples of invasion or distant metastases. (20 refs.)

77-7037 Tumorogenicity of Intraspecific Somatic Cell Hybrids in Nude Mice. (Eng) Aden, D. P. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA 19104); Knowles, B. B. *J Natl Cancer Inst* 58(3): 743-746; 1977.

Intraspecific somatic cell hybrids between normal mouse peripheral blood lymphocytes and a highly tumorigenic L-cell line (Cl-1D) produced tumors in nude mice inoculated sc or ip with 10^7 viable cells. Although the hybrid cells were tumorigenic, both the length of time necessary for tumor appearance and tumor size varied. Neither the growth rate of the parental and hybrid cells in vitro nor their plating efficiency in methylcellulose correlated with the rapidity of tumor growth in vivo. (13 refs.)

77-7038 Early Malignant Transformation of Lymphoid Tissues in Mice Born after a Graft Versus Host Reaction was Induced in Their Mothers. (Rus) Fedosov, E. A. (Smolensk State Medical Inst., Smolensk, USSR); Zarusdin, V. V. *Dokl Akad Nauk SSSR* 236(2): 484-487; 1977.

The early malignant transformation of lymphoid tissues was studied in the offspring of CBA and (CBA x C57BL/6) F_1 female mice in which graft-vs-host reaction (GVHR) had been induced by iv transplantation of 90-180 million live spleen and lymph node cells from C57BL/6 mice during the first or third trimester of pregnancy. CBA females had been mated with C57BL/6 males, (CBA x C57BL/6) F_1 females with CBA or C57BL/6 males. Forty-six offspring died or were killed because of runt diseases during the first 1-2 mo of life. Tumors of the lymphoid tissues (lymph nodes, spleen, and thymus) were found in 32/46 animals, many of which had multiple tumors. Thirty-one young mice showing no signs of runt disease were killed during the first 5-10 days of life; 7 had lymphoid tissue tumors. Twenty-two young mice without signs of runt disease were killed at age 25 days-2 mo; tumors were found in only 2 animals. The mothers of all three groups of offspring had received lymphoid cells during the first trimester of pregnancy. The offspring of females in which

a GVHR was induced in the third trimester of pregnancy were stillborn or they died during the first days of life; tumor incidence was 19/26. Tumor incidence was 0/14 in a control group sacrificed within the first 5 days of life and 0/12 in another control sacrificed within the first 1-2 mo. Tumor development in offspring may be linked to (1) activation of oncogenic viruses in the mother and their passage to the offspring through the placenta and milk or (2) disturbances in the humoral regulation of fetal cell differentiation as a result of maternal GVHR. (12 refs.)

77-7039 Enhanced Osteosarcoma Growth Produced in Rats by Osteosarcoma Allografts. (Eng) Geddes-Dwyer, V. (Dept. Pathology, Univ. Sydney, New South Wales 2006, Australia); Hersey, P.; Cameron, D. A. *Br J Cancer* 35(1): 86-91; 1977.

When male DA rats bearing a ^{32}P -induced osteosarcoma (OS) were treated at the time of tumor induction with allografts of Wistar rat OS, a significant increase in syngeneic tumor wt was noted. This effect was reversed when the allogeneic OS was given 7 days prior to the syngeneic tumor. When the allogeneic OS was given 7 days after the syngeneic tumor, the effect on syngeneic and allogeneic tumor growth was variable. (13 refs.)

77-7040 Induction of Resistance to L1210 Leukemia in BALB/c X DBA/2Cr F₁ Mice, with L1210 Cells Treated with Glutaraldehyde and Concanavalin A. (Eng) Kataoka, T. (Japanese Foundation Cancer Res., Cancer Chemotherapy Center, Div. Experimental Chemotherapy, Kami-ikebukuro, 1-37-1, Toshima-ku, Tokyo, Japan); Oh-hashi, F.; Tsukagoshi, S.; Sakurai, Y. *Cancer Res* 37(4): 964-968; 1977.

Resistance to L1210 leukemia was induced in (BALB/c x DBA/2Cr) F_1 (CD2F₁) mice by preimmunization with tumor cells (1×10^6 ip) pretreated with glutaraldehyde (GA: 0.013%, 0.05%, or 0.2%) and concanavalin A (Con A: 165 $\mu\text{g}/\text{ml}$). After 1 mo the mice were challenged with intact L1210 cells, Con A treated cells, or 0.008% GA/Con A-treated L1210 cells. None of the immunized mice were able to survive the challenge of intact L1210 cells or Con A-treated cells. However, 4/22 mice immunized with 0.013% or 0.05% GA (but not 0.2% GA)/Con A-treated cells were able to survive the challenge of 0.008% GA/Con A-treated L1210 cells. These survivors also were resistant to subsequent step-wise challenges of intact L1210 cells with doses starting at 1×10^3 and increasing to 1×10^6 cells. Pretreatment of the cells with GA before incubation with Con A was required for tumor resistance. GA apparently causes Con A to remain attached to the cell surface. Repeated sensitization with this combination over an 8-day period resulted in higher incidences of survivors than did a single sensitization by equivalent or larger doses. However, five inoculations of 2×10^6

immunogenic cells did not result in greater resistance; therefore, excessively frequent immunizations lead to a low incidence of resistant mice. How cell-bound Con A is associated with induction of tumor resistance is not clear. It may somehow disrupt cell surfaces, thus exposing neoantigen, or it may direct the immune response to cellular antigens and supplement them in their interaction with immunoreactive cells. (13 refs.)

- 77-7041 **Active Immunization Against Spontaneous Tumors in Mice.** (Eng) Patricio, M. B. (Servico de Radio Terapia Do Instituto Portugues de Oncologia, Lisbon, Portugal); Clode, W. H.; Ricardo, J. A. *J Surg Oncol* 9(2): 111-115; 1977.

The incidence of spontaneous tumors was studied in 136 nonirradiated female WHC mice and 138 females exposed to whole-body irradiation (^{60}Co , 400 rads). Mammary tumors developed in 10.2% and lung tumors in 8% of the nonirradiated mice. Of the irradiated mice, 19.5% developed mammary tumors, 21.7% ovarian tumors, 24.5% lung tumors, and 7.9% tumor in other organs. In subsequent experiments, mice were inoculated with fragments of murine mammary or ovarian tumors that had been rejected by hamsters. In 80 nonirradiated mice, immunization reduced mammary tumors incidence to 2.5%. In 79 irradiated and immunized mice, mammary tumor incidence decreased to 8.8% and ovarian tumor incidence, to 3.8%. Lung tumors also declined in the latter group, suggesting that a common factor protected the immunized mice. (8 refs.)

- 77-7042 **Postvaccination Immunity to Marek's Disease.** (Rus) Iakovleva, L. S. (Oncological Res. Center, Acad. Medical Sciences USSR, Moscow, USSR); Mazurenko, N. P. *Vopr Virusol* (3): 331-336; 1977.

Postvaccination immunity to Marek's disease was studied in White Leghorn chickens. The nonpathogenic variant (No. 83) of Marek's disease virus (MDV), Kekawa strain (MDV-Kekawa), was administered to the chickens after 16 or 45 in vitro passages. It made the animals resistant to Marek's disease upon infection with the pathogenic variant (No. 55) of MDV-Kekawa 14 days later. Simultaneous administration of both variants had no protective effect. The cellular interactions between the two variants were studied by virus isolation techniques based on the appearance of genetic markers upon virus passages in chick embryo fibroblast cultures. Both variants were found to persist for a long time in the blood cells; when the nonpathogenic and pathogenic variants were isolated regularly, the titer of the latter was three times lower. The viruses persisted in different cells. Blood cells from chickens infected simultaneously with the two variants contained

equal proportions of both, and both could persist in the same cell. However, if the nonpathogenic virus preceded the pathogenic variant in a cell, it prevented reproduction of the latter. This interference, not mediated by interferon, is believed to play an important role in the postvaccination immunity of chickens to Marek's disease. (11 refs.)

- 77-7043 **The Humoral Immune Response of NIH Swiss and SWR/J Mice to Vaccination with Formalinized AKR or Gross Murine Leukemia Virus.** (Eng) Lee, J. C. (Basic Res. Program, NCI Frederick Cancer Res. Center, Frederick, MD 21701); Ihle, J. N.; Huebner, R. *Proc Natl Acad Sci USA* 74(1): 343-347; 1977.

The humoral immune responses of NIH Swiss and SWR/J mice immunized with formalin-inactivated AKR or Gross murine leukemia virus, respectively, were examined. Both virus vaccines induced had high titers of antibodies detectable in radioimmune precipitation assays using ^3H -leucine-labeled AKR virus and in radioimmunoassays using purified virion components. The predominant antibody titers were directed against gp71 and p15(E). The immune response against gp71 was predominantly type-specific, but the reactivity with p15(E) was predominantly group-specific. A weak immune response against p15 was also detected. Both sera were cytotoxic against cells replicating AKR-Gross virus but not against cells replicating Friend murine leukemia virus. This cytotoxicity could be specifically blocked with purified gp71 of AKR murine leukemia virus. Sera from immune NIH Swiss mice neutralized AKR virus, but did not neutralize Rauscher, Scripps, or wild mouse leukemia virus. (25 refs.)

- 77-7044 **Rejection by Syngeneic Mice of Cell Variants Obtained by Mutagenesis of a Malignant Teratocarcinoma Cell Line.** (Eng) Boon, T. (Cellular Genetics Unit, International Inst. Cellular and Molecular Pathology, avenue Hippocrate, 74, B-1200 Brussels, Belgium); Kellermann, O. *Proc Natl Acad Sci USA* 74(1): 272-275; 1977.

Cells from an azaguanine-resistant malignant teratocarcinoma line (PCC4.azal) were incubated in a medium containing 3 $\mu\text{g}/\text{ml}$ of the mutagen N-methyl-N'-nitro-N-nitrosoguanidine. Twelve of 55 clones isolated from the surviving cells were unable to form tumors in syngeneic 129/Sv mice inoculated sc with $> 5 \times 10^5$ cells. Although these tumorless clones formed tumors as readily as the original cells when they were injected into irradiated mice (600 rads γ radiation), they stimulated the production of radioresistant memory cells that protected immunized animals and conferred resistance by adoptive transfer. Therefore, the inability of the cells to generate progressive tumors was not due to an intrinsic growth defect but to their ability to elicit an immune rejection response in syngeneic hosts. (19 refs.)

- 77-7045 **Characterization of Immune Responses to Spontaneous Hamster Lymphomas.** (Eng) Vasa-Thomas, K. A. (Dept. Microbiology, Univ. Tennessee, Knoxville, TN 37916); Ambrose, K. R.; Bellomy, B. B.; Coggin, J. H. *J Natl Cancer Inst* 58(5): 1287-1293; 1977.

Highly oncogenic cell lines were derived from spontaneous lymphomas that occurred in the third of three lymphoma pizootics in a hamster colony. Immunization of normal hamsters with at least 5×10^6 irradiated lymphoma cells promoted resistance to homologous lymphoma challenge (10^4 viable cells, sc). Only 2/11 immunized and challenged animals developed tumors compared with 100% of nonimmunized animals. Immunization also significantly reduced the incidence of spontaneous lymphomas in hamsters exposed to the contaminated colony. This immunity was transferred in adoptive transfer assays. Resistance to direct challenge was not extended to simian virus 40 (SV40)-induced sarcomas carrying SV40 tumor-specific transplantation antigen nor to herpesvirus-induced carcinoma cells, indicating specificity. The nature of the antigen(s) involved is discussed. (8 refs.)

- 77-7046 **Tumor Immunity to Murine Plasma Cell Tumors. III. Detection of Common and Unique Tumor-associated Antigens on BALB/c, C3H, and NZB Plasmacytomas by In Vivo and In Vitro Induction of Tumor-immune Responses.** (Eng) Burton, R. C. (Walter and Eliza Hall Inst. Medical Res., Royal Melbourne Hosp., Victoria 3050, Australia); Warner, N. L. *J Natl Cancer Inst* 58(3): 601-709; 1977.

Tumor-associated (TAA) were demonstrated on BALB/c, NZB, and C3H mouse plasmacytomas by in vivo and in vitro techniques. By immunizing appropriate F_1 hybrid mice with these tumors, it was possible to show that all the plasmacytomas expressed cross-reactive tumor-associated transplantation antigens. When cytotoxic lymphocytes (CL) were induced in vitro by the coculturing of syngeneic or F_1 hybrid spleen cells with irradiated plasmacytoma cells, shared and unique plasmacytoma TAA were demonstrable. This was accomplished by inducing CL in vitro against one syngeneic plasmacytoma and assaying for lytic activity on a range of ^{51}Cr -labeled BALB/c, NZB, and C3H plasmacytoma cells in vitro. In a second in vitro assay, unlabeled plasmacytoma cells were tested for their ability to inhibit the lysis of a particular ^{51}Cr -labeled plasmacytoma with the use of CL induced in vitro against it. The possibility that these TAA were self antigens was excluded by demonstrating in the inhibition assay that they were not present on the T lymphomas and spleen cells of the same strain and that CL autosenitized in vitro could not significantly lyse ^{51}Cr -labeled plasmacytoma cells in vitro. It is concluded that any one plasmacytoma line possesses multiple TAA of both the shared and unique types. (35 refs.)

- 77-7047 **Cooperation of Immune Lymphoid and Reticuloendothelial Cells During *Listeria***

monocytogenes-mediated tumor Immunity. (Eng) Youdim, S. (Univ. California, San Diego, Dept. Pathology M-012, Sch. Medicine, La Jolla, CA 92093). *Cancer Res* 37(4): 991-996; 1977.

When mixed with cells of a transplantable 3-methylcholanthrene-induced sarcoma, *Listeria monocytogenes* (LM) retarded local tumor development in syngeneic A/He mice. Intrafootpad growth of 10^4 tumor cells was equally inhibited by 4×10^4 admixed LM in normal or LM-immune mice, indicating that concomitant or prior immunity to LM was equally effective in suppressing tumor growth. Development of cellular immunity to viable LM was required for tumor rejection. Mice prevented from developing anti-LM immunity by injection of dead bacteria were also incapable of inhibiting tumor growth. Furthermore, a functionally active reticuloendothelial system was essential for nonspecific inhibition of tumor development, as temporary "paralysis" of the reticuloendothelial system by a prior injection of 10^9 heat-killed LM reduced the effectiveness of LM-mediated tumor inoculated sites revealed the stepwise development of LM-mediated inflammatory reaction associated with gradual degeneration of the adjacent tumor cells. (32 refs.)

- 77-7048 **The Effect of Respiratory Carcinogenesis on Systemic Humoral and Cell-mediated Immunity of Syrian Golden Hamsters.** (Eng) Zwilling, B. S. (Dept. Microbiology, Coll. Biological Sciences, Ohio State Univ., Columbus, OH 43210). *Cancer Res* 37(1): 250-252; 1977.

The effect of 10 weekly intratracheal instillations of 5 mg benzo(a)pyrene (BP) or its noncarcinogenic analog benzo(e)pyrene (BeP) on systemic humoral and cell-mediated immune responses was evaluated in Syrian golden hamsters. Hamsters treated with BP had a transient suppression of the splenic plaque-forming cell response to sheep RBC compared with BeP-treated controls. The numbers of direct (IgM) and indirect (IgG) plaque-forming cells were suppressed during the ninth week of treatment, after which they recovered to normal levels. The results suggest that studies of lymphoid and phagocytic cell function may provide more meaningful information about the immune response of Syrian hamsters during the development of BP-induced bronchogenic carcinomas. (16 refs.)

- 77-7049 **Development of Tumor Cell Resistance to Syngeneic Cell-mediated Cytotoxicity During Growth of Ascitic Mastocytoma P815Y.** (Eng) Biddison, W. E. (Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA 19104); Palmer, J. C. *Proc Natl Acad Sci USA* 74(1): 329-333; 1977.

Cellular and humoral immune responses during progressive tumor growth were studied in DBA/2 mice inoculated ip

with 10^3 viable cells of the syngeneic ascitic mastocytoma P815Y. Peritoneal cells from tumor-bearing hosts were fractionated by velocity sedimentation at unit gravity. Cell-mediated cytotoxicity of fractionated and unfractionated cells was measured by ^{51}Cr -release from tumor target cells. The cell separation procedure revealed significant levels of specific cell-mediated cytotoxicity to P815Y within peritoneal cell populations at 8-16 days after tumor cell inoculation. Tumor cells purified from the peritoneal cell populations of mice inoculated with tumor cells 10 days previously were as susceptible to syngeneic and allogeneic cell-mediated cytotoxicity as P815Y cells grown in vitro. However, tumor cells obtained from mice 16 days after inoculation were resistant to cytotoxicity by syngeneic, but not allogeneic, effector cells. In addition, day 16 tumor cells did not inhibit syngeneic cell-mediated cytotoxicity against P815Y grown in vitro. Immunoglobulin was not detected on day 16 tumor cells and no circulating antibody to P815Y was found in the ascitic fluid of day 16 tumor-bearing mice. These results indicate that tumor cells may escape immune attack by decreased expression of cell surface tumor-associated antigens in the absence of circulating antibody against the tumor. (27 refs.)

- 77-7050 **Comparison of Three Isotopic Assays of Cell-mediated Cytotoxicity Against Mouse Tumor Cells. II. Sensitivity and Specificity of the Assays and Characteristics of Effector and Sensitizing Cells.** (Eng) Ting, C. C. (Lab. Cell Biology, NCI, NIH, Bethesda, MD 20014); Nunn, M. E.; Park, J. Y.; Herberman, R. B. *J Natl Cancer Inst* 58(2): 331-337; 1977.

Three isotopic assays of cell-mediated cytotoxicity [^{51}Cr -release assay (CRA), ^{125}I -iododeoxyuridine-release assay (IRA), and ^3H -proline-release assay (PRA)] were compared under identical test conditions with respect to their sensitivity and specificity and the characteristics of the effector and sensitizing cells. Experiments were performed with effector cells from mice immunized with FBL-3 tumor cells, a syngeneic Friend virus-induced leukemia, or with allogeneic normal spleen cells. Similar results were obtained in all three assays using established tissue culture cells as targets. When short-term culture target cells were used, the IRA gave a more selective pattern of cytotoxicity than did the other two assays. However, when remaining target cells at the end of the assay were treated with trypsin, higher levels of ^{125}I -iododeoxyuridine release were seen and the results were then comparable to those in the CRA and PRA. For assays with short incubation periods, the CRA appeared to be the most suitable. The PRA did not appear to have any particular advantages over the other assays. The IRA may measure a much stronger cytotoxic effect, with the isotope being released only after total cell destruction. There appears, therefore, to be better correlation between the immunologic reaction measured by this assay and in vivo tumor immunity in the FBL-3 system, which may also reflect total destruction of tumor cells. (31 refs.)

- 77-7051 **Spontaneous Cytotoxicity by Human Peripheral Blood Lymphocytes.** (Eng) Nelson, D. L. (Immunophysiology Section, Metabolism Branch NCI, NIH, Bethesda, MD 20014); Bundy, B. M.; Strober, W. In: *Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York: Academic Press, Inc.): 825 pp.; 518-520; 1977.

Subpopulation of lymphocytes from normal healthy volunteers were incubated for 18 hr with ^{51}Cr -labeled Chang liver cell targets in tissue culture medium containing 5% fetal calf serum. The percent ^{51}Cr release was measured to determine effector cell activity. Spontaneous cell-mediated cytotoxicity was increased following macrophage removal, indicating that the effector cell in nonphagocytic, and it only occurred with surface immunoglobulin-negative, Fc receptor-positive lymphocytes. Previous studies have indicated that antibody-dependent cellular cytotoxicity is also mediated by these cells. The search for immune cytotoxic effector cells specific for tumor-associated antigens in human disease is significantly complicated by the presence of such a naturally occurring cytotoxic phenomenon. (4 refs.)

- 77-7052 **Effector Cell Involved in Cell-mediated Cytotoxicity to Cells Infected with Herpes Simplex Virus Type 1.** (Eng) Heron, I. (Inst. Medical Microbiology, Univ. Aarhus, Aarhus, Denmark); Moller-Larsen, A.; Berg, K. *Infect Immun* 16(1): 48-53; 1977.

The characteristics of the effector cells involved in the cell-mediated killing of fibroblasts infected with herpes simplex virus type 1 (HSV-1) were investigated. Suspensions of lymphoid cells from healthy donors were depleted of T-cells, B-cells, cells forming rosettes with sheep WBC (Fc receptors), or cells forming rosettes with bovine RBC coated with rabbit and bovine antibodies and complement 5-deficient mouse serum (complement 3 receptors) by differential centrifugation. Column passage was used as an alternative to depletion of Fc receptors and B-cells. Antibody-dependent cell-mediated cytotoxicity was associated with nonphagocytic cells carrying low-avidity Fc receptors. Some of these had surface immunoglobulins, but others lacked both B- and T-cell markers. Low killing levels were found without added HSV-1 antibodies, and this killing seemed to depend on cells belonging to the same subpopulation as the antibody-dependent effector cells. (20 refs.)

- 77-7053 **Cell-mediated Cytotoxicity to Herpes-infected Cells in Humans: Dependence on Antibodies.** (Eng) Moller-Larsen, A. (Inst. Medical Microbiology, Univ. Aarhus, Aarhus, Denmark); Heron, I.; Haahr, S. *Infect Immun* 16(1): 43-47; 1977.

Herpes simplex virus type 1 (HSV-1)-infected human skin fibroblasts were used as target cells in a ^{51}Cr -release assay in which peripheral blood mononuclear cells from HSV seropositive and seronegative donors were the effector cells. Cytotoxicity was exerted by ordinarily prepared lymphoid cells, but it could be reduced by extensive washing of the effector cells. The antibody dependence of the system was shown by the recovery of activity through the addition of positive serum or medium used for the early washes of effector cells. Three donors found to be seronegative in the usual serological tests were shown to be seropositive in this test. It is proposed that the assay can be used as a very sensitive serological test. (13 refs.)

77-7054 **Cold Lymphocytotoxic Antibodies in Nasopharyngeal Carcinoma.** (Eng) Lamelin, J. P. (Unité Biologique Carcinogénèse, Inst. Agency Res. Cancer, 150 Cours Albert Thomas, 6908, Lyon, France); Revillard, J. P.; Chalopin, J. M.; Ho, J. H.; Souissi, T.; Schwabb, G., De-The, G. *Br J Cancer* 35(4): 426-432; 1977.

In the presence of complement and at 15 C, sera from 98 patients with nasopharyngeal carcinoma (NPC), a disease associated with Epstein-Barr virus (EBV), were cytotoxic for human lymphocytes with a higher frequency than that of matched controls. The cold lymphocytotoxic antibodies (LTA) responsible for this activity had the same properties as those described in sera from individuals with acute viral infections. The frequency and geometric mean titers of LTA varied with patient origin (Chinese > North African > Caucasian) and stage of disease (Stage IV > Stage I). A positive correlation between LTA and anti-EBV titers was found with regard to antibodies to viral capsid antigen and EBV nuclear antigen. The absence of correlation between LTA and antibody titers to EBV early antigen probably reflects the complex relationships between viral infection and LTA production, but it is compatible with the hypothesis that LTA acts as an immune regulator in viral infections. (30 refs.)

77-7055 **Antibodies to the R Component of Epstein-Barr Virus-induced Early Antigens in Burkitt's Lymphoma Exceeding in Titer Antibodies to Epstein-Barr Viral Capsid Antigen.** (Eng) Henle, W. (Div. Virology, Joseph Stokes, Jr., Res. Inst., Children's Hosp. Philadelphia, 34th and Civic Center Blvd., Philadelphia, PA 19104); Henle, J. *Natl Cancer Inst* 58(3): 785-786; 1977.

The correct Epstein-Barr anti-viral capsid antigen (VCA) titer was determined in highly restricted (R) reactive sera by means of EB3 cells of Burkitt's lymphoma (BL) origin. Two groups of sera were used: (1) sera from 40 BL patients that had yielded anti-R titers with acetone-fixed Epstein-Barr virus (EBV)-superinfected RAJI cell smears that had closely matched the anti-VCA titers, and (2) sera from 40 BL patients without detectable antibodies to the R component and

sera from 20 patients with anti-VCA titers well in excess of the anti-R titers. These sera were titrated in indirect immunofluorescence tests with smears of EB3 cells fixed in acetone or methanol. Since the R component, but not VCA, was found to be denatured by methanol fixation, the parallel use of acetone- and methanol-fixed EB3 cells permitted determination of the correct anti-VCA titer. The anti-R titers of BL patients were up to eightfold higher than the anti-VCA titers. Anti-R titers equalling or exceeding anti-VCA titers appear to be unique for African BL, and, at present, no explanation can be offered for the high anti-R titers seen in this disease. (7 refs.)

77-7056 **Genetic Control of Antinuclear Antibodies in Mice Infected with Rauscher Leukemia Virus.** (Eng) Varet, B. (Batiment Gustave Roussy-27, Rue du Faubourg Saint Jacques, 75674 Paris Cedex 14, France); Cannat, A.; Gisselbrecht, S. *Cancer Res* 37(4): 1115-1118; 1977.

The incidence of antinuclear antibodies after Rauscher leukemia virus (RLV) inoculation was significantly higher in C57BL/6 than in BALB/c mice and still greater in their F_1 hybrids. The relationships among antinuclear antibody incidence, erythroblastic disease, RLV production, and *H-2* genotypes were studied in the F_1 generation and backcrosses using different virus inocula. Susceptibility to erythroblastic disease appeared to be intermediate in the hybrids, which were sensitive at the higher dose but relatively resistant at the lower dose. Among the backcrosses, 28% of C57BL/6 x (C57BL/6 x BALB/c) mice given the higher dose were sensitive vs 43.5% expected, and 68% of BALB/c x (C57BL/6 x BALB/c) mice receiving the lower doses were sensitive vs 48.5% expected. The results suggest that (1) at least two genes are involved in the control of susceptibility to RLV-induced erythroblastosis, one of them probably being *H-2* linked, and that (2) a non-*H-2*-linked gene seems to control, at the same time, induction of antinuclear antibodies, focus-forming virus production in the spleen, and susceptibility to the disease. It can be concluded that C-type viruses play an active role in antinuclear antibody induction. (25 refs.)

77-7057 **Selective Inhibition of Cell Growth and Associated Changes in Glycolipid Metabolism Induced by Monovalent Antibodies to Glycolipids.** (Eng) Lingwood, C. A. (Div. Biochemical Oncology, Fred Hutchinson Cancer Res. Center, Seattle, WA 98104); Hakomori, S. *Exp Cell Res* 108(2): 385-391; 1977.

The effect of glycolipids on regulation of the cell cycle and cell proliferation, and the absence of this regulation in transformed cells were investigated. BALB/3T3 cells and their Kirsten murine sarcoma virus-transformed derivatives, and

NIL2K cells and their polyoma virus-transformed (NILpyT) cells) were used in the experiment. Cells were treated with purified antiglycolipid antibodies, then with ^{125}I -labeled "protein A" (specific to the Fc immunoglobulin region). Transformation did not significantly alter the expression of globoside and N-acetylhematoside (GM_3) although the relative degree of exposure was increased. NIL2K and NILpyT cells had G1 peaks for anti- GM_3 and antigloboside; peaks for these antibodies were also seen during G2. These peaks were greater in transformed cells than their normal counterparts. In the 3T3 and Kirsten cells, the G1 peak was not clear but in G2 was greater for transformed cells. Low concentrations of antibody to GM_1 lowered the growth rate of normal cells without affecting the transformed derivatives. This inhibition could be removed by antiserum pretreatment with liposomes containing GM_1 . Within 4 hr of Fab anti- GM_1 treatment, an increase was observed in ganglioside labeling with sparse cells. Both hematosides GM_2 and GM_1 were unaffected by antibody treatment. When similarly treated cells were harvested at early confluency, GM_1 labeling and GD1a labeling were enhanced relative to control cultures. When cells were harvested at full confluency, the labeling was reduced relative to controls. Kirsten cells showed no alteration in ganglioside labeling. It is suggested that a carbohydrate moiety on normal cells can trigger growth arrest and that the same moiety on transformed cells is insensitive to inhibition. (41 refs.)

- 77-7058 **Chemoattractant Properties of *Corynebacterium parvum* and Pyran Copolymer for Human Monocytes and Neutrophils.** (Eng) Majeski, J. A. (Surgical Immunobiology Lab., Dept. Surgery, Univ. Cincinnati Medical Center, Cincinnati, OH 45267); Stinnett, J. D. *J Natl Cancer Inst* 58(3): 781-783; 1977.

Preliminary observations are reported that both pyran copolymer and *Corynebacterium parvum* vaccine generate substances chemotactic for human monocytes and neutrophils in the presence of serum. The WBC and monocytes were obtained from healthy male donors, and the serum was type AB. In the absence of serum, neutrophils and monocytes did not migrate toward either pyran or *C. parvum*, but in the presence of serum, concentrations as low as $1\text{ }\mu\text{g}$ of either of these preparations were able to generate chemotactic factors. Both agents were as effective as endotoxin (lipopolysaccharide B, *Salmonella typhosa* 0901) in generating serum chemotaxins, but neither was synergistic with endotoxin in eliciting a migratory response. When heat-inactivated human serum was used, the migratory response of neutrophils to endotoxin-generated chemotaxins was $< 50\%$ of that seen with unheated serum. A similar reduction was observed when $10\text{ }\mu\text{g/ml}$ pyran was the chemoattractant. In contrast, the migratory response to *C. parvum* ($10\text{ }\mu\text{g/ml}$) was unaffected by the use of heated serum. These results suggest that the generation of chemotactic factors by pyran involves the heat-labile comple-

ment sequence in normal serum, whereas *C. parvum* vaccine does not require complement to generate chemotactic factors. The chemotaxins were not specific for either monocytes or neutrophils. (10 refs.)

- 77-7059 **Characterization of Macrophage Chemotaxins in Tumor Cell Cultures and Comparison with Lymphocyte-derived Chemotactic Factors.** (Eng) Meltzer, M. S. (Div. Cancer Biology and Diagnosis, Immunobiology Program, Lab. Immunobiology, Immunopathology Section, NIH, NCI, Bethesda, MD 20014); Stevenson, M. M.; Leonard, E. J. *Cancer Res* 37(3): 721-725; 1977.

Culture fluids from several methylcholanthrene-induced fibrosarcomas (1023, 1037, 1038, and 1063) were chemotactic for C3H/HeN mouse syngeneic peritoneal macrophages in vitro. Macrophages from BCG-infected mice were more responsive to tumor-derived chemotaxis than normal macrophages. The response of peritoneal granulocytes from BCG-infected mice to chemotaxis was not significantly different from the granulocyte response to culture medium. Supernatants from proliferating spleen cell cultures stimulated by phytohemagglutinin or concanavalin A did not induce detectable levels of chemotactic activity. The chemotactic activity of the cultures paralleled cell growth, with max activity occurring during the log phase. Sephadex G-100 chromatography of the culture supernatants resulted in a single peak of chemotactic activity in the 15,000-mol wt region. On DEAE-cellulose, the chemotactic activity eluted in a specific conductance region of 7.5 mmho/cm. Biologically and physico-chemically, the chemotactic activity of the tumor culture fluids was different from mouse lymphocyte-derived chemotactic factor (LDCF). LDCF showed a major peak of activity in the 40,000-mol wt region and about 15 mmho/cm specific conductance, and it did not correlate with cell proliferation in vitro. Chemotactic factors released by tumors and/or rapidly proliferating cells may provide a mechanism for macrophage accumulation. However, this accumulation at a tumor site may not necessarily indicate an effective antitumor response, and, therefore, a macrophage chemotaxin released by tumor cells could result in cell destruction or cell proliferation. (19 refs.)

- 77-7060 **Inhibition of Macrophage Chemotaxis by Neoplastic and Other Rapidly Proliferating Cells In Vitro.** (Eng) Normann, S. J. (Dept. Pathology, Univ. Florida Coll. Medicine, Gainesville, FL 32610); Sorkin, E. *Cancer Res* 37(3): 705-711; 1977.

Certain culture supernatants of rapidly proliferating cells were found to inhibit the chemotactic migration of macrophages while weakly attracting polymorphonuclear WBC

(PMN). Culture supernatants of 3T3 murine fibroblasts, SV40-transformed 3T3, Chinese hamster ovary fibroblasts, dimethylbenzanthracene-induced rat neoplasms, and polyoma virus-induced rat neoplasms were collected after 24, 48, and 72 hr of cell growth. At serial dilutions of up to 1:10,000, none of the five culture supernatants demonstrated chemotactic activity for rat macrophages, but they were weakly attractive for PMN. Macrophage chemotaxis was suppressed when a strong chemotactic attractant (heated rat serum) was mixed in equal proportions with the culture supernatants. This effect was greatest for polyoma virus-induced rat neoplasms and least for 3T3 murine fibroblasts. An even greater suppressive effect was obtained when culture supernatants were added directly to the cells. Since washed macrophages were inhibited to the same degree as unwashed cells, it was concluded that the inhibitory substance(s) bound onto the macrophage cell surface. This ability of rapidly proliferating cells in culture to generate substances inhibitory to macrophage chemotaxis while attracting PMN may be related to the mechanism by which tumor cells induce a cell-specific defect in chronic, but not acute, inflammation in the host. Rapidly proliferating cells may be capable of altering the macrophage component of the host defense mechanism. (29 refs.)

77-7061 **Induction of Liver Tumors by 3'-Methyldimethylaminoazobenzene (3'-Me-DAB) in Rats Chronically Infected with Toxoplasma or Besnoitia.** (Eng) Frenkel, J. K. (Dept. Pathology and Oncology, Univ. Kansas Medical Center, Kansas City, KS 66103); Reddy, J. *J Reticuloendothel Soc* 21(1): 61-68; 1977.

Beginning on the 36th day after sc infection with *Toxoplasma gondii* or *Besnoitia jellisoni*, male Fisher 344 rats were fed a diet that included the carcinogen 3'-methyldimethylaminoazobenzene (3'-Me-DAB) for 19 wk. At 14 wk, 2/4 uninfected 3'-Me-DAB-treated controls showed liver tumors, but none were found in the infected rats. After 19 wk, tumors also began to appear in infected rats. After another 15 wk on a regular diet, almost all carcinogen-treated rats (infected and uninfected) had hepatocellular carcinoma and about one-third had cholangiocarcinoma. Although tumor induction time was prolonged, previous infection with the protozoa did not alter the final tumor incidence. The possible delay of tumor development by activated macrophages is discussed. (18 refs.)

77-7062 **Receptors for IgG: Subclass Specificity of Receptors on Different Mouse Cell Types and Definition of Two Distinct Receptors on a Macrophage Cell Line.** (Eng) Heusser, C. H. (Basel Inst. Immunology, Basel Switzerland); Anderson, C. L.; Grey, H. M. *J Exp Med* (5): 1316-1327; 1977.

Subclass specificity and aggregate size requirements of IgG receptors on normal and transformed mouse cells were evaluated by measuring the binding of radiolabeled monomeric and bis-diazotized benzidine (BDB)-aggregated mouse myeloma proteins fractionated by gel filtration. Monomers [(IgG)1], tetramers [(IgG)4], and high-mol wt (HMW) aggregates [(IgG)100] were used. Three patterns of reactivity were observed. (1) Macrophage and macrophage-like cell lines (P388 and J774) bound monomer IgG2a preferentially, and HMW IgG aggregates bound as follows: IgG1 = IgG2b = IgG2a. (2) Lymphoid lines D2N and S49 showed no binding affinity for monomer IgG2a, and HMW aggregates bound as follows: IgG1 = IgG2b > IgG2a. (3) Other Thy-1 positive lymphoid cell lines (EL4 and L5178) and normal T and B cells showed no ability to bind monomer IgG, and HMW aggregates bound as follows: IgG1 > IgG2b ≥ IgG2a. Thus, macrophage-like cells carry two distinct receptors for IgG, one capable of binding IgG2a and another capable of binding all aggregates. Analysis of the inhibitory capacity of different IgG subclasses on the binding of aggregated IgG and monomer IgG2a to P388 cells and trypsinization experiments supported this concept. (17 refs.)

77-7063 **Relationship of Surface Immunoglobulin-bearing Cells, Plasma Cells, and Tumor Development in Anaplastic Carcinoma-bearing A/J Mice.** (Eng) Chi, D. S. (Dept. Human Biological Chemistry and Genetics, Shriners Burns Inst., Univ. Texas Medical Branch, Galveston, TX 77550); Harris, N. S. *Cancer Res* 37(4): 1119-1124; 1977.

Surface immunoglobulin (Ig)-bearing cells and plasma cell antigen (PCA)-bearing cells were studied during growth of the A/J 15091A anaplastic carcinoma in syngeneic mice. Peripheral blood was collected every other day from normal and carcinoma-bearing mice. Lymphocytes obtained by Ficoll-Hypaque density centrifugation were assayed for Ig- and PCA-bearing cells using either fluorescein-conjugated goat antimouse Ig or rabbit antimouse plasma cell serum and fluorescein-conjugated goat anti-rabbit Ig. A marked increase in Ig bearing cells from tumor-bearing mice was observed by day 6, and it peaked at day 10. An increase in PCA-bearing cells followed the Ig-bearing cell increase by 2 to 4 days. The Ig-bearing cells declined by day 12, but the PCA-bearing cells remained elevated through day 20. Using rabbit antimouse plasma cell serum as an immunosuppressive agent, a 4-day prolongation of the mean survival time was observed in rabbit antimouse plasma cell serum-treated tumor-bearing mice. This suggests that tumor growth in this model may be related to an active humoral immune response and that suppression of the plasma cell population may prove to be beneficial in the treatment of certain tumors. (25 refs.)

77-7064 **Lymphocytes Suppressing Both Immunoglobulin Production and Erythroid Differentiation in Hypogammaglobulinaemia.** (Eng) Litwin, S. D. (Div. Human

Genetics, Dept. Medicine, Cornell Univ. Medical Coll., New York, NY); Zanjani, E. D. *Nature* 266(5597): 57-58; 1977.

Lymphocytes from two patients (S1 and S2) diagnosed as having immunodeficiency with thymoma were studied. S1 was in remission from RBC agenesis, but S2 was hematologically normal. Cultured S1 and S2 lymphocytes produced much less immunoglobulin (Ig) than normal lymphocytes, and they blocked Ig production by normal B lymphocytes in cocultivation studies. These defects were due to a failure to secrete Ig and not to an inability to synthesize it. S1 had greater suppressor activity than S2 in single and cocultivation studies. When erythropoietin (2 IU) was added to normal human bone marrow several hundred erythroid colonies were formed. Serum from S1 or S2 did not significantly alter the number of erythroid colonies, but mononuclear cells from normal subjects enhanced colony formation significantly. In contrast, addition of S1 or S2 lymphocytes decreased the number of colonies formed, with S1 being more suppressive. When adherent cells were removed from S1 or S2, there was no loss of suppression in either the Ig production or plasma clot system. Thus, lymphoid cells that interfere with the maturation of human erythroid precursors and B lymphocytes in culture are present in the blood of two patients with immunodeficiency with thymoma. (20 refs.)

- 77-7065 Reduced Incidence of Marek's Disease Gross Lymphomas in T-Cell-depleted Chicken.** (Eng) Sharma, J. M. (U.S. Dept. Agriculture, Agricultural Res. Service, North Central Region, Regional Poultry Res. Lab. 3606 E. Mount Hope Road, East Lansing, MI 48823); Nazerian, K.; Witter, R. L. *J Natl Cancer Res* 58(3): 689-692; 1977.

Line 7 chickens, which are highly susceptible to Marek's disease (MD), were depleted of T cells by neonatal thymectomy, total-body γ irradiation with 600 rads on day 2, and inoculations with anti-T-cell serum on days 2, 5, and 8. They were inoculated with MD virus (MDV) on day 13, and on day 41, the experiments were ended. In two replicate experiments, T-cell-depleted chickens developed a significantly lower incidence of gross lymphomas than did intact controls that were simultaneously inoculated with MDV (89% vs 20%, $p < 0.05$ and 82% vs 0%, $p < 0.01$). The incidence of gross lymphomas in the T-cell-depleted group that was reconstituted with syngeneic cells on day 11 was higher than in the T-cell-depleted group (28% vs 0%, $p > 0.05$). Microscopic lesions of MD containing a heterogeneous population of lymphoid cells were found in all birds, regardless of initial treatment. The intensity of the lesions in the T-cell-depleted and in the B-cell-depleted, reconstituted groups was lower than that in the intact group. Both T and B cells were present in all lymphomas, although T cells predominated (61.4% vs 14.11%). These results suggest that T cells may have two roles in the development of MD: they may serve as a target for formation of lymphomas by MDV and

they may participate in immune surveillance against the disease in resistant chickens. It was concluded that the residual T-cell population in the T-cell-depleted chickens participated in lymphoma formation. (23 refs.)

- 77-7066 Inhibition of Mammary Tumors by Incomplete T-Cell Depletion.** (Eng) Roubinian, J. R. (Clinical Immunology, Rheumatology Section, Veterans Admin. Hosp., San Francisco, CA 94121); Blair, P. B. *J Natl Cancer Inst* 58(3): 727-734; 1977.

The effects of neonatal and perinatal thymectomy on mammary tumorigenesis in (C57BL x I)F₁C3H hybrid female mice were determined. When hybrid females were neonatally thymectomized by controlled suction, a procedure that removes thymic lobes completely, a large proportion of animals developed a fulminant wasting disease and died before tumors developed. However, when hybrid females were subjected to neonatal thymectomy by continuous suction, a procedure that results in retention of thymic remnants, they survived and manifested a significant prolongation of the latent period before tumorigenesis. When complete removal of the thymus was carried out in the perinatal period, the effect on mammary tumorigenesis was critically dependent on age at surgery. The procedure was without effect when performed at 1, 3, and 8 wk of age. However, when it was performed at 9-12 days of age, there was a delay or a decrease in the appearance of mammary tumors. The extent of T-cell depletion and/or its timing in relationship to the introduction of murine mammary tumor virus appeared to be crucial factor in eventual tumor development. (26 refs.)

- 77-7067 Recognition of a Naturally Occurring Idiotypic by Autologous T Cells.** (Eng) Julius, M. H. (Basel Inst. Immunology, 487 Grenzacherstrasse, Postfach 4005 Basel 5, Switzerland); Augustin, A. A.; Cosenza, H. *Nature* 265(5591): 251-253; 1977.

Recognition of the naturally occurring idiotype of autologous T cells was studied by generating these cells in BALB/c mice. The mice were inoculated at birth with 0.1 ml of A/J anti-T15 serum. When 3×10^6 dinitrophenyl (DNP)-primed B cells mixed with 10×10^6 T15-primed splenic T cells were transferred iv into irradiated (600 rads) recipients, the response was 2,340 indirect anti-DNP plaque-forming cells (PFC)/spleen, 15 times higher than the background response of 142 calculated by summing the responses obtained by transfer of the same cell populations separately. T cells from the same T15-primed suppressed animals did not provide any detectable helper activity above the background level. When 2×10^6 or 10×10^6 splenic T cells from T15-primed suppressed mice were transferred with 3×10^6 DNP-primed splenic B cells to suppressed recipients

(to eliminate higher levels of immunoglobulin), the anti-DNP PRC responses were 50 and 20 times higher than the background response, respectively. These T cells were specific for the T15 idotype. It is suggested that high levels of the T15 idotype in conventional BALB/c mice might partially mask T15-specific T-cell clones. Since conventional mice produce anti-T15 antibodies, T15-specific precursor cells are present but are not expressed to the same extent as in suppressed mice. If mature T15-specific helper T cells exist in unprimed suppressed BALB/c mice, there are too few to be detected and/or antigen-dependent proliferation and maturation of precursor cells might be required for the generation of helper activity. (13 refs.)

77-7068 Separation of Tumor Enhancing Murine Thymocytes by Agglutination with a Peanut Lectin (PNA). (Eng) Linker-Israeli, M. (Dept. Chemical Immunology, Weizmann Inst. Science, Rehovot, Israel); Itzhaki, M.; Umiel, T.; Trainin, N.; Sharon, N. In: *Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York: Academic Press, Inc.): 825 pp.; 515-517; 1977.

Thymic lymphocytes (2×10^7) mixed with 3LL (2.5×10^5) tumor cells in a 80:1 ratio and injected sc into syngeneic C3H/eb x C57BL/F₁ mice enhanced tumor growth, whereas splenocytes delayed growth. Similar results were obtained when thymocytes were injected along with either Rauscher leukemia virus-induced thymoma cells in C57BL/6 mice or benzo(a)pyrene-induced fibrosarcoma cells in C3H/eb mice. Immature (A) thymocytes were separated from mature thymocytes by agglutination with PNA, a peanut lectin. When the separated fractions were admixed with 3LL cells and injected into syngeneic recipients, the PNA-agglutinable A thymocytes significantly enhanced tumor growth. This effect was confined to adherent A thymocytes which represent about 5% of the A thymocytes. (4 refs.)

77-7069 A Modified Host-mediated Assay Using Cultured Human Lymphoid Cells in Diffusion Chambers in Mice and Cytogenetic Effects of Cyclophosphamide. (Eng) Huang, C. C. (Dept. Experimental Biology, Roswell Park Memorial Inst., Buffalo, NY 14263). *Environ Res* 3(2): 267-277; 1977.

A modified host-mediated assay system using cultured human lymphoid cells as target cells is described. The human cells are cultured in diffusion chambers (DC) and implanted into C₃H/St mice. Induction of chromosome aberrations in human cells in DC and in host bone marrow cells is used as an index of mutagenicity of a given compound and its

metabolites. Of six human lymphoid lines (2 from Burkitt's lymphoma patients, 1 from a Down's syndrome patient, 3 from normal subjects) studied for their growth potential in DC in mice, two of the normal lines failed to grow. The other four lines proliferated well. When injected sc into mice at doses of 40, 80, or 160 mg/kg, cyclophosphamide induced a high incidence of chromosome aberrations in host bone marrow cells and in the cells of the two human lines tested in DC: a normal diploid line and a Burkitt's lymphoma line. The majority of aberrations were chromatid breaks and chromosome fragments. The Burkitt's lymphoma line was more sensitive to cyclophosphamide than the normal cell line. (18 refs.)

77-7070 Primary In Vitro Sensitization of Isogeneic and Allogeneic Murine Lymphocytes to Normal and SV40-transformed BALB/c 3T3 Cells. (Eng) Maki, T. (Dept. Microbiology and Immunology SUNY Downstate Medical Center, Brooklyn, NY 11203); Howe, M. L. In: *Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York: Academic Press, Inc.): 825 pp.; 403-405; 1977.

Murine BALB/c lymphocytes were cultured for 5 days on monolayers containing varying numbers of mitomycin-C-treated isogeneic untransformed BALB/c 3T3 cells or simian virus 40 (SV40)-transformed 3T3-B cells (SV3T3-B). Max cytotoxicity occurred in cultures containing 5×10^6 BALB/c lymphocytes and 5×10^4 SV3T3-B cells. Testing of a variety of target cells demonstrated that the BALB/c effector cells are preferentially reactive with the H-2d SV3T3-B cells. Untransformed cells failed to generate cytotoxicity. Max responses of allogeneic CBA lymphocytes occurred with both types of stimulator cells at a concentration of 5×10^4 . The data suggest that the induction of tumor-associated antigens on SV3T3-B cells results in a significant reduction in the expression of normal histocompatibility antigens. This sensitization technique may provide a model system for the study of cellular events underlying the response of lymphocytes to tumor cells. (1 ref.)

77-7071 Preservation of In Vitro Biological Functions in Regional Lymph Node Lymphocytes in Squamous Head and Neck Cancer. (Eng) Saxon, A. (Dept. Microbiology and Immunology, Immunobiology Group, Univ. California at Los Angeles Sch. Medicine, Los Angeles, CA 900024); Portaro, J. *Cancer Res* 37(4): 1159-1164; 1977.

Regional lymph node lymphocytes from patients with squamous cancer of the head and neck were tested in vitro for their ability to proliferate in response to phytohemagglutinin (PHA), concanavalin A, and allogeneic stimuli in one-way mixed-lymphocyte culture. Their ability to act as cytotoxic

effectors in PHA-dependent cellular cytotoxicity was also evaluated, and all results were compared with normal lymph node or blood lymphocytes. The regional lymph node lymphocytes retained proliferative capabilities equal to those in control lymph nodes or blood, but they were unable to mediate PHA-dependent cellular cytotoxicity. This was not a tumor-related effect, because normal lymph node lymphocytes were also ineffective in this assay. The failure of the regional immune response to control early tumor growth could not be accounted for by generalized nonspecific immunosuppression in regional lymph node lymphocytes, as these cells demonstrated normal in vitro activity. (19 refs.)

- 77-7072 Lymphoid Subpopulation Changes in Regional Lymph Nodes in Squamous Head and Neck Cancer.** (Eng) Saxon, A. (Dept. Microbiology, Univ. California at Los Angeles Sch. Medicine, Los Angeles, Ca 90024); Portis, J. *Cancer Res* 37(4): 1154-1158; 1977.

Lymph nodes from 10 normal patients and regional lymph nodes (RLN) from 19 patients with squamous cancer of the head and neck were evaluated for their lymphoid subpopulations. Compared with normal lymph nodes, RLN from cancer patients demonstrated a marked increase in the proportion of cells with membrane immunoglobulin, the receptor for the third component of complement, and the receptor for the Fc portion of IgG. The increased Fc receptor cells were not Fc-bearing T-lymphocytes, since they separated with the nonsheep RBC-lymphocyte rosette-forming population. The overall T-lymphocyte percentage in RLN was proportionally decreased. A transition from the normal lymph node composition to the altered lymphocyte profile seen in RLN was demonstrated on moving from distal lymph nodes to RLN within the lymphatic drainage of a tumor. Lymph nodes involved with tumor also showed the pattern of bursa-equivalent cell population increases. (33 refs.)

- 77-7073 Immunologic Studies in Chronic Lymphocytic Leukemia: Defective Stimulation of T-Cell Proliferation in Autologous Mixed Lymphocyte Culture.** (Eng) Smith, J. B. (Inst. Cancer Res., Fox Chase Cancer Center, Philadelphia, PA 19111); Knowlton, R. P.; Koons, L. S. *J Natl Cancer Inst* 58(3): 579-585; 1977.

Peripheral blood WBC from untreated patients with chronic lymphocytic leukemia (CLL) and normal age- and sex-matched controls were tested for their ability to increase DNA synthesis following mixed lymphocyte culture (MLC) with homologous and autologous lymphocytes. The responder cells were unfractionated mononuclear cells from peripheral blood (PBL) or T-cell enriched populations obtained by filtration on a nylon wool column. Unfractionated mononuclear PBL from both normal controls and CLL patients responded to alloantigenic stimulation by increased

DNA synthesis. This proliferative response was enhanced by removing the adherent cells from the responding cells. When normal cells provided the allogeneic stimulus for T-cell-enriched fractions from CLL patients, adherent cell fractions caused more DNA synthesis than did T-cell-enriched populations. However, when cells from CLL patients were the allogeneic stimulus, adherent fractions caused greater DNA synthesis than did T-cell enriched fractions in only 3/6 experiments. T-cell enriched fractions from normal controls showed increased proliferation following culture with autologous mitomycin C-treated adherent cell fractions. In contrast, when nonadherent cells from CLL patients were cultured with autologous T-cell-enriched fractions, this phenomenon did not occur. This lack of response was not due to serum factors or to short-range factors produced by inactivated CLL cells in culture. This lack of autorecognition in CLL may indicate the monoclonal nature of the B cells in this disease or a defect in helper or suppressor T cells. The breakdown of autorecognition could be an important pathogenic event in the development of CLL. (33 refs.)

- 77-7074 T and B Lymphocyte Antigen-positive Null Cell Leukemias.** (Eng) Kaplan, J. (Children's Hosp. Michigan, 3901 Beaubien Blvd., Detroit, MI 4820); Ravindranath, Y.; Peterson, W. D. *Blood* 49(3): 371-378; 1977.

Rabbit antisera to the autologous T- and B-lymphoblast cell lines HSB-2 and SB were tested for their reactivity with leukemic cells from 16 children with T-, B-, or null cell acute lymphoblastic leukemia (ALL) and 3 children with acute myelogenous leukemia (AML). Reciprocal absorption experiments demonstrated that the T- and B-lymphocyte antigens detected by these antisera occurred on two distinct subpopulations of peripheral blood null cells, one expressing T antigens and the other expressing B antigens. Lymphoblasts from 4/4 patients with T-cell leukemia and 2/10 with null cell leukemia expressed T-cell but not B-cell antigens. Blasts from 8/10 patients with null cell leukemia, 1 patient with B-cell leukemia, and 3/3 patients with AML expressed B-cell but not T-cell antigens. The results indicate that there are two distinct types of null leukemias and that ALL can be more accurately classified by combining markers such as E-rosette formation, surface immunoglobulin, and complement receptors with serologically defined T- and B-lymphocyte markers. (34 refs.)

- 77-7075 Hairy Cell Leukemia: B-Lymphocyte and Phagocytic Properties.** (Eng) Utsinger, P. D. (Div. Rheumatology and Clinical Immunology, Univ. North Carolina Sch. Medicine, Chapel Hill, NC 27514); Yount, W. J.; Fuller, C. R.; Logue, M. J.; Orringer, E. P. *Blood* 49(1): 19-27; 1977.

The neoplastic cells of three patients with hairy cell leukemia were studied. The cells resynthesized IgM and IgD after tryp-

inization, bore aggregate or Fc receptors, and phagocytosed latex particles. However, the cells did not demonstrate non-specific esterase activity. Stimulation by phytohemagglutinin (PHA) resulted in minimal ^3H -thymidine incorporation, and < 9% of the stimulated cells entered an interphase or tetraploid state. This abnormal mitogen response was largely restored when the patients' purified T lymphocytes were cultured with PHA. Hairy cells cultured with normal allogeneic mononuclear cells did not undergo blast transformation. The data strongly suggest that the cells of some hairy cell leukemia patients are B lymphocytes with phagocytic capabilities. (43 refs.)

77-7076 **Lymphocyte Blastogenic Responses to Allogeneic Leukocytes and Autochthonous Tumor Cells in Colorectal Carcinoma.** (Eng) Jubert, A. V. (Oncology Dept., St. Mary's Hosp., 200 Jefferson Ave. SE, Grand Rapids, MI 49503); Talbott, T. M.; Mazier, W. P.; MacKeigan, J. M.; Campos, M. M.; Muldoon, J. P.; Benjamin, H.; Ferguson, J. A.; Bowman, H. E. *J Surg Oncol* 9(2): 171-178; 1977.

Peripheral blood lymphocytes (PBL) and mesenteric lymph node lymphocytes (LNL) from 36 patients with colorectal cancer were tested for their blastogenic reactivity against normal allogeneic WBC and autochthonous tumor cells. The activity correlated with the patients' Dukes classification. Mesenteric LNL reacted significantly better than PBL to allogeneic WBC in both Dukes B and C. There were too few patients in Dukes A and D to permit statistical evaluation, but the trend was the same. By contrast, LNL failed to react to autochthonous tumor cells in all classes, except in a few Dukes B patients. The proportion of PBL reactivity to autochthonous tumor cells seemed to increase for Dukes C and D. Specific lymphocyte reactivity in colorectal carcinoma may be related to the antigenicity and immunogenicity of the tumor. (16 refs.)

77-7077 **Changing Erythrocyte Populations in Juvenile Chronic Myelocytic Leukemia: Evidence for Altered Regulation.** (Eng) Dover, G. J. (Dept. Pediatrics, Johns Hopkins Hosp., Baltimore, MD 21205); Boyer, S. H.; McKham, W. H.; Kazazian, H. H.; Pinney, D. J.; Sigler, A. *Am J Med* 49(3): 355-365; 1977.

Fetal and adult RBC characteristics were studied serially in a 10-mo-old girl with juvenile chronic myelocytic leukemia. At presentation the RBC exhibited predominantly fetal characteristics as indicated by 69% HbF, 1.1% HbA₂, absent I antigen, and fetal levels of the RBC enzymes carbonic anhydrase I and II, glucose-6-phosphate dehydrogenase, pyruvate kinase and lactate dehydrogenase; 90% of the RBC contained HbF. However, Orskov-Stewart hemolysis demonstrated that at least one adult characteristic was present. Seven mo later

HbF was 17% and I antigen and carbonic anhydrase I had increased to adult levels. The number of cells containing HbF had decreased to 30%. At least three new populations of RBC were present after 7 mo. Two of these populations exhibited a mixture of both fetal and adult characteristics, which suggested an ongoing disturbance of regulatory mechanisms in RBC. (36 refs)

77-7078 **Human B-Lymphocyte Antigens Expressed by Lymphocytic and Myelocytic Leukemia Cells. II. Detection by Human Anti-B-Cell Alloantisera.** (Eng) Billington, R. (Dept. Surgery, Sch. Medicine, Univ. California, Los Angeles, CA 90024); Ting, A.; Terasaki, P. I. *J Natl Cancer Inst* 58(2): 199-203; 1977.

A polymorphic antigen normally expressed by most human lymphocytic and myelocytic leukemia cells has also been found on peripheral blood B lymphocytes and cultured lymphoblastoid B-cell lines. To investigate and identify these B-cell specificities, 34 samples of human sera from multiparous women were tested against three rabbit anti-B-cell antisera directed against leukemia cells, B lymphocytes, and cultured lymphoblastoid B-cell lines by complement-dependent cytotoxicity assays. The 34 human anti-B-cell alloantisera reacted with the B cells and cultured B-cell lines plus most of the myelocytic and lymphocytic leukemia cells. It was possible to identify two groups of leukemia cells on the basis of reactivity to the anti-B-cell antisera. There was a positive group of 14/18 acute myelocytic leukemia cells, 10/13 acute lymphoblastic leukemia cells, 4/6 chronic myelocytic leukemia cells, and 2/2 chronic lymphocytic leukemia cells tested. This group of leukemia cells also showed reactivity to rabbit anti-B-cell sera produced by papain digests of spleen cell membranes. F(ab')₂ fragments of the rabbit antisera were able to block specifically the reactions of human antisera against B cells and leukemia cell. Thus, the antigen detected by the rabbit anti-B-cell serum was identical to or closely related to the antigen detected by the human serum, a conclusion supported by immunoprecipitation data. (22 refs.)

77-7079 **Extraction of Ia-like Antigen from Cultured Human B Lymphoblasts and Its Expression on Leukemic Cells.** (Eng) Sullivan, A. K. (Dept. Experimental Medicine, McGill Univ., Montreal, Canada); Jerry, L. M.; Rowden, G.; Rode, H. N.; Gordon, J.; Thi, H. L.; Shea, M. In: *Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York: Academic Press, Inc.): 825 pp.; 406-408; 1977.

A method is described whereby a 32,000- to 36,000-mol-wt membrane glycoprotein with immunologic and functional characteristics similar to the murine Ia antigens was rapidly isolated from 10⁹ human B lymphoblastoid NC37 cells. When

assayed by indirect immunofluorescence, these antigens showed preferential reactivity with B lymphocytes and minimal reaction with T cells. Expression of the Ia-like antigens on the leukemic cells of 14 patients with chronic lymphocytic leukemia (B-type) was consistently high. However, their variable expression, especially in acute leukemias, indicates a broader role in hemopoietic cell differentiation. (5 refs.)

- 77-7080 Antigen-induced Locomotor Responses in Lymphocytes.** (Eng) Wilkinson, P. C. (Dept. Bacteriology and Immunology, Univ. Glasgow, Glasgow, Scotland); Parrott, D. M.; Russell, R. J.; Sless, F. *J Environ Med* 145(5): 1158-1168; 1977.

The effect of protein antigens on the locomotion of lymphocytes from the lymph nodes draining the site of antigenic challenge in immunized mice and from the same nodes in control mice was studied with the use of filters. A checkerboard assay in which the absolute concentration and the concentration gradient of attractant were varied in a series of chambers was also incorporated. Bovine or human serum albumin was chemokinetic for unimmunized lymphocytes since the extent of cell migration into the filters varied with the absolute concentration of albumin, but not with the concentration gradient. Thus, serum albumin influenced the rate but not the direction of locomotion. Ovalbumin and nonalbumin proteins did not show this effect. Using the same assay, the migration of primed lymphocytes in the presence of the priming antigen was shown to be influenced by the antigen gradient in a way that suggested a positive chemotactic response of the lymphocytes to antigen. This response was demonstrated clearly only when the cells were in a chemokinetic medium containing serum albumin. (12 refs.)

- 77-7081 Naturally Occurring Lymphocyte Reactivity to Purified Mammary Tumor Virus Antigens.** (Eng) Gillette, R. W. (Meloy Labs., Inc., 6715 Electronic Drive, Springfield, VA 22151); Lowery, L. T. *J Reticuloendothel Soc* 21(1): 1-6; 1977.

When pulsed at various time intervals with ³H-thymidine, spleen cells from both high (RIII and C3H/He) and low (NIH Swiss) mammary tumor virus (MTV)-expressing murine strains reacted in vitro to MTV antigens prepared from RIII milk. Spleen cells from newborn RIII and C3H mice did not respond to MTV. In direct and indirect migration inhibition assays, spleen cells were also incubated at 37 C with MTV antigens at a 1:40 dilution, which was shown to stimulate lymphocytes maximally. Spleen cells from tumor-bearing females significantly inhibited macrophage migration when tumors were small (< 0.5 g). However, spleen cells from donors with large tumors (> 1.5 g) were often hyporeactive to MTV antigens. The results indicate that there is a high level of specific immunity to MTV throughout life and that MTV tumors progress in the face of this immunity. (17 refs.)

- 77-7082 Preparation of Cell-free Feline Oncornavirus-associated Cell Membrane Antigen.** (Eng) Wolff, L. H. (Dept. Veterinary Pathobiology, Ohio State Univ., Columbus, OH 43210); Olsen, R. G.; Hoover, E. A.; Yohn, D. S.; Schaller, J. P. *J Natl Cancer Inst* 58(3): 791-793; 1977.

Cell-free feline oncornavirus-associated cell membrane antigen (FOCMA) was prepared from cell line FL-74, which was derived from a lymphoid neoplasm of a strain Kawakami-Theilen feline leukemia virus (FeLV)-infected cat. Antigen yields were quantitated by inhibition of complement-dependent antibody-mediated cytotoxicity using reference antiserum from a cat that had regressed sarcoma. Subcellular fractions of FL-74 cells were obtained from sucrose density gradients and assayed for FOCMA by cytotoxicity inhibition. The light membrane fraction, which contained the highest specific activity, was observed by electron microscopy to be largely free of ribosomal and particulate material as well as virus particles. The gradient fraction containing the most antigenic activity was characterized by heavier bilayered plasma membranes complexed with cytoplasmic material, and it was contaminated with mitochondria and ribosomes. A soluble preparation obtained by proteolytic enzyme digestion of the crude membrane fraction of FL-74 cells also was capable of cytotoxic inhibition. None of the fractions inhibited undiluted and unabsorbed reference serum, which produced 100% lysis of target cells. Thus, by using this assay, antigen could be separated from cells in association with membranous material and could be recovered in soluble form from papain digests of crude membranes. (18 refs.)

- 77-7083 Common Tumor Rejection Antigens in Methylcholanthrene-induced Squamous Cell Carcinomas of Mice Detected by Tumor Protection and a Radioisotopic Footpad Assay.** (Eng) Economou, G. C. (Hellenic Anticancer Inst., St. Savas Hosp., Athens, Greece); Takeichi, N.; Boone, C. W. *Cancer Res* 37(1): 37-41; 1977.

Seven transplantable lines (LSQ-2,-3,-6,-7,-10,-12, and -15) of squamous cell carcinomas of the skin, induced in BALB/c mice by painting with 3-methylcholanthrene, were screened for cross-reactivity of their tumor-rejection antigens (TRA). TRA cross-reactivity was detected by reduced tumor frequency and tumor wt following tumor cell challenge and by a radioisotopic footpad assay for delayed hypersensitivity against viable tumor cells. Each LSQ line was immunogenic against and/or immunosensitive to at least one and usually more than one of the other lines. More than two antigens appeared to be present in the lines. These results indicate a close equivalence between antigens that induce a delayed hypersensitivity reaction in the footpad and those that induce immunity to tumor cell challenge. As opposed to chemically induced connective tissue tumors (sarcomas), chemically in-

duced epithelial tumors (carcinomas) appear to share common TRA. Because cross-reactivity increased with increasing number of transplant passages, it is suggested that these shared antigens were not present on the primary tumors, but they appeared later in connection with cell membrane changes secondary to loss of differentiation. The successful use of the footpad assay to detect cross-reacting TRA of chemically induced squamous cell carcinomas may provide a rationale for the screening of human patients with squamous cell carcinomas for cross-reacting TRA. (16 refs.)

- 77-7084 Expression and Thermal Stability of Simian Virus 40 Tumor-specific Transplantation Antigen and Tumor Antigen in Wild Type- and *tsA* Mutant-transformed Cells.** (Eng) Anderson, J. L. (Lab. Molecular Biology, Nat. Inst. Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD 20014); Chang, C.; Mora, P. T.; Martin, R. G. *J Virol* 21(2): 459-467; 1977.

The expression and thermal stability of simian virus 40 tumor-specific transplantation antigens (TSTA) and tumor antigens (TA) were studied in wild-type- and temperature-sensitive (*ts*)-transformed cells. A *ts* mutant (A28-RE) that loses TA during exposure to the nonpermissive temperature was also found to lose TSTA. In contrast, a typical *tsA*-transformed line (A239-MB) expressed both TA and TSTA at the nonpermissive temperature. Complement fixation tests showed that TA in lysates from A239-MB cells were three to four times more thermolabile at either 33 or 40 C than TA from wild-type-transformed cells. In contrast to TA, TSTA assayed in vitro by tumor rejection were thermostable. High levels of TSTA and tumor-specific surface antigens were present even after 24 hr incubation of the extracts at 50 C, but the TA of wild-type- and *tsA* mutant-transformed lines lost their activity in < 10 and 4 min, respectively. Since these surface antigens were also thermostable when they were obtained from cells transformed by *tsA* mutants, they could not be distinguished from the wild-type antigens. These results indicate a coordinate expression of TA and TSTA in transformed cells, confirm that TA are virus-encoded, and confirm that the antigenic and immunogenic determinants that characterize TA and TSTA activities are distinct. The possibility that TSTA are of viral origin cannot be excluded. (33 refs.)

- 77-7085 Isolation of Tumor-associated Antigen(s) from a Moloney Virus Induced Leukemia (MBL-2).** (Eng) Ng, A. K. (Lab. Immunodiagnosis, NCI, NIH, Bethesda, MD 20014); McIntire, K. R.; Braatz, J. A.; Herberman, R. B. In: *Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York: Academic Press, Inc.): 825 pp.; 1977.

Two in vitro assay methods, one humoral and one cell-mediated, are used to monitor the isolation of tumor-associated antigen(s) from MBL-2, a Moloney virus-induced ascitic lymphoma of C57BL/6 mice. In the humoral assay, inhibition of ^{51}Cr -release cytotoxicity by specific cytotoxic antibodies and complement can be performed. In the cell-mediated assay, antigen preparations can be tested by incubating them with splenocytes from murine sarcoma virus-inoculated C57BL/6 mice, for the production of macrophage migration inhibitory factor. Antigens extracted by the 3 M KCl method or recovered from the supernatant of the MBL-2 ascitic fluid have shown reactivity in both assays. (6 refs.)

- 77-7086 Immunity to MCA-induced Rat Sarcomas: Analysis of In Vivo and In Vitro Results.** (Eng) Harmon, R. C. (Immunogenetics Group, Dept. Microbiology and Immunology, Univ. California at Los Angeles, Los Angeles, CA 90024); Clark, E. A.; Reddy, A. L.; Hildemann, W. H.; Mullen, Y. *Int J Cancer* 20(5): 748-758; 1977.

Immunity to three methylcholanthrene (MC)-induced sarcomas (FMF1, FMM2, and FMM3) was studied in male F344 Fischer rats. Resistance to tumor challenge with 5×10^5 FMM3 tumor cells was examined after excision of primary FMM3 tumors. There was a significant decrease in tumor incidence in all groups of immunized rats; resistance did not decrease over 240 days. There was similar resistance to the FMF1 tumor in FMF1-excised rats and to the FMM2 tumor in FMM2 rats. There was no evidence for cross-reactive tissue-associated antigens to the three sarcomas. However, secondary FMM3 tumor growth challenge was significantly inhibited in rats immunized with both FMM2 and FMM3. The Winn assay of passive tumor neutralization indicated that rats receiving FMM2 or FMM3 tumor cells admixed with hyperimmune spleen cells showed inhibition of tumor growth only if the spleen cell donors had been immunized with the respective tumors. No significant inhibition of FMF1 hyperimmune spleen cells was noted. Repetition of the assay using spleen cells from rats whose tumors had been excised 10 days prior to the assay indicated that postexcision of spleen cells can be effective in passive tumor neutralization without prerequisite hyperimmunization of donors. Concomitant immunity was observed only in rats bearing FMM2 or FMM3 primary tumors and FMM2 or FMM3 secondary tumors. In vitro, however, FMM3 tumor-immune rats were not selectively cytotoxic for cultured FMM3 target cells. In the Winn assay, spleen cell cytotoxicity in vitro did not correlate with tumor protection in vivo; normal spleen cells were cytotoxic against cultured sarcoma target cells in vitro, and they inhibited tumor growth in vivo. Thus, induced anti-tumor reactivity was only demonstrable in vivo. (35 refs.)

- 77-7087 Tumor-associated Antigens in H-2 Hemizygous Isoantigenic Variants of a Somatic Cell Hybrid, Derived from the Fusion of a 3-Methylcholanthrene-induced**

Sarcoma and a Mammary Carcinoma. (Eng) Klein, G. (Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm 60, Sweden). *J Natl Cancer Inst* 58(2): 383-386; 1977.

Reciprocal isoantigenic variants derived from TA3Ha/MSWBS hybrid cells were examined to investigate the concept that 3-methylcholanthrene (3-MC)-induced, sarcoma-associated, tumor-specific transplantation antigens (TSTA) could be modified H-2 antigens. The hybrid was produced by fusing the TA3Ha mammary carcinoma of strain A origin (H-2a) with the 3-MC-induced MSWBS sarcoma (H-2s). MSWBS expresses a strong TSTA that induces a rejection reaction in the syngeneic A.SW host. The genetic determinants of the H-2 complex are localized on chromosome 17. TA3Ha contributes two normal chromosomes 17 to the hybrid, whereas both chromosomes 17 of MSWBS are localized on readily identifiable translocations (17/1 and 17/M1). It was demonstrated that the two strain A-compatible variants that have lost the sarcoma-derived chromosomes 17 still contained the same TSTA as the two reciprocal strain A.SW-compatible variants that have lost the mammary carcinoma-derived H-2 chromosomes. These results eliminate the possibility that 3-MC-induced TSTA is a modified form of H-2 or that its structural determinant(s) is localized on chromosome 17. (14 refs.)

77-7088 Resistance Genes to Murine Leukemia in the I Immune Response Gene Region of the H-2 Complex. (Eng) Lonai, P. (Dept. Chemical Immunology, Weizmann Inst. Science, Rehovot, Israel); Haran-Ghera, N. *J Exp Med* 146(4): 1164-1168; 1977.

A resistance to leukemogenesis in mice by A-RadLV, a variant of radiation leukemia virus, is described. This locus, *Rrv-1*, was mapped to subregions I-A, I-B, and I-J of the H-2 histocompatibility complex. It is suggested that *Rrv-1* may be in complementation with a second locus to the right of the complex, between *Rrv-1* and *H-2D*. This localization and the complementation of the two loci for resistance are characteristics of *Ir* genes, which indicates a possible relationship between the genetic regulation of immune response and susceptibility to leukemia. (13 refs.)

77-7089 Role of the Major Histocompatibility Complex in Resistance to Marek's Disease: Restriction of the Growth of JMV-MD Tumor Cells in Genetically Resistant Birds. (Eng) Longenecker, B. M. (Dept. Immunology, Univ. Alberta, Edmonton, Alberta, Canada); Pazderka, F.; Gavora, J. S.; Spencer, J. L.; Stephens, E. A.; Witter, R. L.; Ruth, R. F. *Adv Exp Med Biol* 88: 287-298; 1977.

Forty populations of chickens from all over the world were typed for the B^{21} allele, which is associated with resistance to Marek's disease (MD). Serological testing demonstrated the B^{21} alloantigen in 12 populations, and its presence was confirmed in 10/10 populations, tested by the graft-vs-host response (GVH). The 12 populations with the B^{21} allele represent the extreme production types of the species: White Leghorn, Rhode Island Red, Black Australorp, Fayoumi, and Red Jungle Fowl, the progenitor of the species. The XP line of the White Leghorn breed was chosen to confirm the association of B^{21} with resistance to MD. When progeny of the B^{21}/B^{21} and B^2/B^2 sublines were challenged at hatching with an allogeneic transplantable lymphoma of MD (the JMV tumor cell line), death occurred within 18 days in 13.3% and 37.1% of the populations, respectively. Apparently, JMV cells grow more slowly in a genetically resistant B^{21} environment than in a genetically susceptible B^2 environment. Furthermore, JMV cells were characterized as a transplant of B_1 carrying lymphoblastoid cells, which may indicate an allele with susceptibility to MD. The JMV tumors may represent a genetic accident that discriminates the private serologic antigen of a B allele from its major histocompatibility determinants. This would eliminate the signal by which the host would first recognize the JMV tumor as foreign, and it may be all that is necessary to provide the circumstances in which tumorigenesis does not depend on the complete viral genome. (22 refs.)

77-7090 Expression of H-2 Specificities and of MuLV Envelope Antigens on Murine Tumors. (Eng) Schirmacher, V. (Institut für Immunologie und Genetik, Deutsches Krebsforschungszentrum, Heidelberg, W. Germany); Garrido, F. In: *Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D.O., ed. (New York: Academic Press, Inc.) 825 pp.; 379-381; 1977.

Long-term transplanted tumors of different etiology and origin were regularly passaged in syngeneic mice. Collected ascites tumor cells were tested for the expression of cell-surface antigens in a newly designed postlabeling radioassay using H-2 alloantisera and a goat antiserum against the highly purified envelope glycoprotein GP71 of murine (Friend) leukemia virus (MuLV). Typing of 10 different murine tumor cell lines with 24 H-2 alloantisera (240 reactions) resulted in 48 cases of unexpected additional reactivities. Absorption experiments showed that this anomalous antitumor activity in some sera was probably not directed against MuLV antigens. On tumor cells, anti-H-2 sera may detect new specificities that are similar to or cross-reactive with normal H-2 specificities of certain haplotypes. (8 refs.)

77-7091 Isolation of Polyoma Virus-induced Surface Antigens in Hamster Cells: Potassium Chloride Solubilization and Differential Precipitation. (Eng) Barra, Y. (Unit 119, Institut National de la Sante et de la Recherche Medicale, 27 Bd Le Roure, 13009 Marseille, France); Astier, A. M.; Meyer, G. *J Natl Cancer Inst* 58(3): 721-726; 1977.

Surface antigens were extracted in soluble and active form with 3 M KCl from a polyoma virus-induced hamster fibrosarcoma and from hamster embryo cells. They were tumor-specific transplantation antigens (TSTA), as shown by tumor rejection, and a surface (S) antigen, as demonstrated by the inhibition of surface fluorescence on living polyoma virus-transformed cells. The extracts were fractionated by salting out with $(\text{NH}_4)_2\text{SO}_4$. In tumor cell extracts, all TSTA activity and a part of S-antigen activity were found in the fraction precipitated with 60% saturation in $(\text{NH}_4)_2\text{SO}_4$. Another part of S-antigen activity was found in the fraction precipitating at 80% saturation in tumor cell extracts. The

precipitate at 60% saturation of embryonic cell extracts also had a part of S-antigen activity. Receptor site activity for concanavalin A was also retained after solubilization, and it was confined to the 40% saturation $(\text{NH}_4)_2\text{SO}_4$ precipitate in the case of tumor and embryonic cell extracts. (22 refs.)

See also:

- *(Rev.): 77-6609, 77-6637, 77-6646, 77-6647, 77-6648, 77-6649, 77-6650, 77-6651.
- *(Chem.): 77-6843, 77-6847, 77-6853, 77-6876.
- *(Phys.): 77-6908, 77-6912.
- *(Viral): 77-6935, 77-6938, 77-6947, 77-6949, 77-6957, 77-6958, 77-6966, 77-6972, 77-6976, 77-6991, 77-6992, 77-6993, 77-7019.
- *(Path.): 77-7121, 77-7127, 77-7132, 77-7141, 77-7143.

PATHOGENESIS

- 77-7092 **Regulation of the Secretory Cycles of Mucous and Serous Cells in the Human Bronchial Gland.** (Eng) Coles, S. (Dept. Experimental Pathology, Cardiothoracic Inst., Brompton Hosp., Fulham Road, London, SW3 6HP, England). *Adv Exp Med Biol* 89: 155-168; 1977.

Factors controlling the synthesis and secretion of bronchial mucus were studied in human bronchial glands in organ culture. The secretory cycle of mucous and serous cells differed: the former alternately accumulated and discharged secretory material, but in the latter synthesis and discharge occurred simultaneously. Parasympatho-mimetic agents (methacholine, physostigmine) increased the secretory rate of mucous and serous cells by stimulating discharge, but they had no effect on the rate of precursor incorporation into intracellular glycoproteins. Glycoprotein synthesis inhibitors (cycloheximide, salicylate) reduced the incorporation of precursors into intracellular macromolecules but not the discharge of preformed glycoproteins. Ouabain reduced glucose and threonine incorporation into mucous and serous cells; it had no effect on glucosamine incorporation or the discharge rate. Ouabain-sensitive threonine transport, but not glucose transport, increased in hypertrophied glands. Exposure of rats to tobacco smoke increased the size of the tracheal and laryngeal glands and the secretory rate of mucous cells. These effects were prevented by the anti-inflammatory agent phenylmethyloxadiazole, which reduced mucous cell secretory activity. (27 refs.)

- 77-7093 **Bronchogenic Carcinoma in Three Siblings.** (Eng) Jones, F. L. (Dept. Thoracic Medicine, Geisinger Medical Center, Danville, PA 17821). *Bull Geisinger Med Cent* 29(2): 23-25; 1977.

Case reports are presented for two sisters and a brother who developed carcinoma of the lung at the relatively early ages of 39, 40, and 43 yr. All three had a long history of heavy cigarette smoking. Each of the three patients had metastases at the time of diagnosis, documented by biopsy in two and in the third by the behavior of the tumor, with death from cerebral metastases occurring in < 6 mo. Lung cancer had been suspected in the father, but he had refused studies and his death was attributed to coal-worker's pneumoconiosis. These findings indicate that although environmental agents are of prime importance in the pathogenesis of lung cancer, carcinogens may interact potently with a genetic factor. The smoking first-degree relatives of patients with lung cancer are at high risk of developing bronchogenic carcinoma. (7 refs.)

- 77-7094 **Intranuclear Tubular Structures Observed in the Cells of an Alveolar Cell Carcinoma of the Lung.** (Eng) Torikata, C. (Dept. Pathology, Keio Univ., Sch. Medicine, Shinano-machi 35, Shinjuku-ku, Tokyo, Japan). Ishiwata, K. *Cancer* 40(3): 1194-1201; 1977.

Electron microscopic observations of adenocarcinoma cell from the lung of a 56-yr-old non-smoking woman are presented. The most unusual finding was the presence of intranuclear tubular structures that corresponded to eosinophilic nuclear inclusions that were apparent light microscopically. These structures were found in about 50% of the tumor cell and in no other cell types, and were only seen in the nucleus. They consisted of a single membrane with an electron-dense central core and were similar to a type of structure previously reported in the literature. A sarcoid-like reaction occurred in the cancer stroma, possibly as an immunologic response to substances released from the tumor. It is suggested that the tubular structures could be of viral origin; further studies are necessary to substantiate this observation. (31 refs.)

- 77-7095 **Cancerous Alveolitis Against a Background of Chronic Pneumonia.** (Rus) Smirnov, E. A. (V.N. Rozanov Central District Hosp., Pushkino, Moscow District, USSR). *Vopr Onkol* 23(6): 20-26; 1977.

Cancerous alveolitis and bronchiolitis were diagnosed post mortem in three men with chronic pneumonia and diffuse pulmonary sclerosis. The patients died 4-6 mo after manifestation of the symptoms. This form of lung cancer accounted for 2.4% of all lung cancers. The findings indicate that diffuse pulmonary sclerosis creates favorable conditions for the formation of metaplasia and anaplasia of the alveolar and bronchiolar epithelial cells in foci of chronic pneumonia, leading to the development of squamous cell carcinoma. (13 refs.)

- 77-7096 **Alveolar Cell Carcinoma in Identical Twins: Similarity in Time of Onset, Histochemistry and Site of Metastasis.** (Eng) Joishy, S. K. (Div. Genetics, Dept. Medicine, Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY 14642); Cooper, R. A.; Rowley, P. T. *Ann Intern Med* 87(4): 447-450; 1977.

Case reports of two identical twins, aged 58 yr, with alveolar cell carcinoma of the lung and brain metastasis are presented.

The carcinoma had a similar time of onset in both patients and the histochemistry of the tumors was similar. It is suggested that shared genes determined not only the susceptibility of pulmonary cells to neoplastic transformation, but also the character of the resultant neoplasm. (21 refs.)

77-7097 The Morphology of Human Papillomas of the Upper Respiratory Tract. (Eng.) Incze, J. S. (Dept. Pathology, Tufts Univ. Medical Sch., Boston, MA); Lui, P. S.; Strong, M. S.; Vaughan, C. W.; Clemente, M. P. *Cancer* 39(4): 1634-1646; 1977.

Results are presented of a 3-yr-study of recurrent squamous papillomas of the upper respiratory tract in 97 patients. Examination by light and electron microscopy showed that the morphology of these papillomas did not differ essentially from uninvolved mucosa. The spinous cells formed a layer much thicker than normal. Hindered desquamation in conjunction with chronic inflammation may cause the epithelial overgrowth. (20 refs.)

77-7098 Pulmonary Metastases from Basal-cell Carcinoma of Skin. (Eng) Sakula, A. (Redhill General Hosp., Redhill, Surrey RH1 6LA, England). *Thorax* 2(5): 637-642; 1977.

A 54-yr-old man died of pulmonary metastases from a basal cell carcinoma of the forehead 19 yr after the carcinoma was diagnosed at the site of a minor trauma scar. The cancer recurred several times over the period following diagnosis. Autopsy confirmed the metastatic nature of the tumor. The literature is reviewed. (29 refs.)

77-7099 Histogenesis of Dermatofibrosarcoma Protuberans. (Rus) Ol'khovskaia, I. G. (Dept. Pathological Anatomy Human Tumors, Oncological Scientific Center, Acad. Medical Sciences USSR, Moscow, USSR); Rubins, A. S. *Arkhh Patol* 39(5): 33-37; 1977.

Electron microscopy of dermatofibrosarcoma protuberans removed from three patients revealed large amounts of collagen fibers in the interstitial space and elongated cells with clusters of microfibrils around the membrane. The rough endoplasmic reticulum was well-developed and at times broadened, and it contained fine granules. The nuclei were round, regularly shaped or indented. The nuclear chromatin was distributed homogeneously. Dense nucleoli and intranuclear bodies were frequently seen in the nuclei. The cells resembled normal fibroblasts, which suggests a fibroblastic origin of the tumor. The well-developed rough endoplasmic reticulum and the nuclear bodies are indicative of high metabolic activity in the tumor cells. (21 refs.)

77-7100 Tibial Adamantinoma: Its Histogenesis from Ultrastructural Studies. (Eng) Yoneyama, T. (Laboratory Service, 113, Veterans Admin. Hosp., Salem, VA 24153); Winter, W. G.; Milsow, L. *Cancer* 40(3): 1138-1142; 1977.

The results of light and electron microscopic studies on a tibial adamantinoma removed from a 44-yr-old man are presented. The presence of microfilament bundles and tight cell junctions, the absence of a transition between tumor and endothelial tissue and the lack of vesicular transport, microvilli, or basement membranes suggested that this tumor was not derived from endothelial or pericytic elements. It is suggested that it could have arisen from ameloblastic cells of the oral cavity, synovial cells, mesothelial cells or epithelial cells derived from the skin; the pros and cons of each of these hypotheses are discussed. (16 refs.)

77-7101 An Ultrastructural Study of the Calcifications in Calcifying Odontogenic Cysts and Odontomas. (Eng) Sapp, J. P. (Dept. Pathology, Univ. Western Ontario, London, N6A 5B7, Ontario, Canada); Gardner, D. G. *Oral Surg* 44(5): 754-766; 1977.

The light and electron microscopic findings are presented on epithelial calcifications associated with the calcifying odontogenic cyst and the odontoma. Three types of calcifications were noted: dystrophic spherical calcifications, spherical calcifications possibly composed of dysplastic enamel, and diffuse calcifications probably representing dysplastic dentin or cementum. (27 refs.)

77-7102 An Ultrastructural Study of Eosinophilic Granuloma: The Langerhans Cell-Its Role in Histogenesis and Diagnosis. (Eng.) Cutler, L. S. (Dept. Oral Biology, Univ. Connecticut Health Center, Farmington, CT 06032); Krutchkoff, D. *Oral Surg* 44(2): 246-252; 1977.

An electron microscopic study of a case of eosinophilic granuloma of the mandible demonstrated the presence of histiocytes containing intracytoplasmic inclusion bodies structurally indistinguishable from Langerhans granules. These inclusion bodies were composed of parallel membranes with a diameter of 400-450 Å separated by a central density with a diameter of 100 to 110 Å (and a periodicity of 75 Å). Some of the inclusion bodies had a "racquet", "paddle", or "dumb-bell" shape. The eosinophils at the lesion were ultrastructurally normal, except for their content of several highly osmophilic bodies not commonly seen in typical eosinophils. The Langerhanslike cells are believed to be mesenchymal in origin, and their presence may be diagnostic of eosinophilic granuloma. (28 refs.)

- 77-7103 Mucosal Changes in the Gastric Stump 20-25 Years after Partial Gastrectomy.** (Eng.) Schrumpf, E. (Res. Lab. Gastroenterology, Ulleval Hosp., Oslo, Norway); Stadaas, J.; Myren, J.; Serck-Hanssen, A.; Aune, S.; Osnes, M. *Lancet* 2(8036): 467-469; 1977.

Mucosal changes were observed in the gastric stump 20-25 yr after partial gastrectomy in most of the 108 patients examined. Histological examination of biopsy material revealed infiltrating carcinoma in four patients and severe dysplasia (carcinoma in situ) in three. Only one patient had near-normal mucosa close to the anastomosis; in the remainder, the gastric remnant showed various degrees of dysplasia, metaplasia, or chronic atrophic gastritis. Malignant or premalignant (severe dysplastic) changes were found in 28/226 biopsy specimens taken from patients with cancer and severe dysplasia. Patients who have had partial gastrectomy for benign lesions are at high risk of gastric stump carcinoma. (10 refs.)

- 77-7104 Esophageal Cancer Occurring after Early Gastric Cancer, and Examination of Other Double Cancers at These Sites.** (Eng) Nakada, K. (Dept. Surgery, Cancer Inst. Hosp., Japan); Kinoshita, I.; Ohashi, I.; Ohta, H.; Nishikubo, K.; Takagi, K. *Jpn J Cancer Clin* 23(13): 1246-1251; 1977.

An early esophageal cancer was found during x-ray examination of a patient who had undergone gastrectomy 2 yr previously for early gastric cancer. Among 17 cases of double esophageal and gastric cancer treated over a 20-yr period, 9 were synchronous and 8 were asynchronous. Of the stomach cancers coexisting with esophageal cancer, five were early cancers. In the eight asynchronous cases, esophageal cancer developed after surgery for stomach cancer in six cases and gastric cancer developed after surgery for esophageal cancer in the remaining cases. (12 refs.)

- 77-7105 The Gardner Syndrome: A Family Study in Cell Culture.** (Eng) Danes, B. S. (Lab. Cell Genetics, Dept. Medicine, Johns Hopkins Hosp., Baltimore, MD 21205); Krush, A. J. *J Natl Cancer Inst* 58(3): 771-775; 1977.

The occurrence of tetraploidy was studied in skin cultures of epitheloid and fibroblastic cells from 137 members of six families with the Gardner syndrome (3 classical, 3 variant). Increased tetraploidy was observed in cultures from all 28 clinically affected family members and from 19/50 normal members at risk for inheriting the Gardner gene. Cultures from 56/59 family members not at risk did not show increased tetraploidy. Although the six families studied fell into two clinical groups, the 28 affected individuals were indistinguishable on the basis of tetraploidy in their skin cultures.

Follow-up clinical studies will establish whether the Gardner gene can be identified through cell culture studies. (13 refs.)

- 77-7106 Biliary Cystadenoma and Cystadenocarcinoma: Report of 14 Cases and Review of the Literature.** (Eng.) Ishak, K. G. (Div. Hepatic Pathology, Armed Forces Inst. Pathology, Washington, DC 20306) Willis, G. W.; Cummins, S. D.; Bullock, A. A. *Cancer* 39(1): 322-338; 1977.

The clinical and pathologic features and long-term follow-up of eight patients with biliary cystadenoma and six patients with biliary cystadenocarcinoma are reported, and the previous literature is reviewed. All the cystadenomas were in middle-aged women, but the six cystadenocarcinomas occurred in both men (4) and woman (2). Most of the patients with cystadenoma and one-half of those with cystadenocarcinoma presented with an abdominal mass. Four of the patients whose cystadenoma was excised are alive and well for periods ranging from 2.5-13 yr. Two of the patients with cystadenocarcinoma have survived for 3 and 3.7 yr, respectively, after subtotal hepatic lobectomy. Morphologically, the cystadenocarcinomas differ from the cystadenomas in that the former have cellular pleomorphism and anaplasia and infiltration of the underlying fibrous stroma. They can invade adjacent viscera, and they may occasionally metastasize to distant sites. The presence of benign epithelium in most cystadenocarcinomas supports their origin from cystadenomas. (50 refs.)

- 77-7107 Carcinogenesis in the Pancreas. I. Long-term Explant Culture of Human and Bovine Pancreatic Ducts.** (Eng) Jones, R. T. (Dept. Pathology, Sch. Medicine, Univ. Maryland, Baltimore, MD 21201); Barrett, L. A.; van Haaften, C.; Harris, C. C.; Trump, B. F. *J Natl Cancer Inst* 58(3): 557-565; 1977.

Human and bovine pancreatic ductal explants were cultured for 60 and 85 days, respectively, with good ultrastructural preservation. The explants also incorporated radioactive precursors into protein, RNA, and DNA. Although the cultured ducts did not exhibit reversible cell injury, they showed sublethal alterations such as the formation of numerous autophagic vacuoles and residual bodies and the accumulation of large lipid droplets. The results demonstrate that explant cultures can be used to study the induction of pancreatic neoplasms by chemical carcinogens. (21 refs.)

- 77-7108 Differences in Growth of Transplants of Liver, Liver Hyperplastic Nodules, and Hepatocellular Carcinomas in the Mammary Fat Pad.** (Eng) Williams,

G. M. (Naylor Dana Inst. Disease Prevention, 1 Dana Road, Valhalla, NY 10595); Klaiber, M.; Farber, E. *Am J Pathol* 89(2): 379-390; 1977.

Transplantation of fragments of normal rat liver autologously and isologously into the inguinal mammary fat pad of male Fischer rats permitted survival of up to 75% of the grafts for 38 wk, the longest interval studied. Similarly transplanted hepatocarcinomas grew rapidly and progressively in this site. Neither autologous or isologous transplants of liver hyperplastic nodules displayed obvious growth, although like normal liver, they also persisted for up to 38 wk. Some persisting hyperplastic cells retained certain characteristic features, but others appeared to revert to a normal morphology. Thus, there is a stage in which hyperplastic cells do not possess the progressive growth ability of neoplastic cells and appear to be capable of reversion to a normal phenotype. (44 refs.)

77-7109 α -Fetoprotein-containing Cells in the Early Stages of Liver Carcinogenesis Induced by 3'-Methyl-4-dimethylaminoazobenzene and 2-Acetylaminofluorene. (Eng) Tchipsheva, T. A. (Cancer Res. Center, Acad. Medical Sciences, USSR, Moscow, USSR); Guelstein, V. I.; Bannikov, G. A. *Int J Cancer* 20(3): 388-393; 1977.

White, random-bred, and Wistar rats were given the carcinogens 3'-methyl-4-dimethylaminoazobenzene and 2-acetylaminofluorene in the diet, and the changes in liver morphology were noted. Hepatocytes were damaged, large numbers of hyperplastic nodules were seen, and transitional cell proliferation increased. Indirect immunofluorescence revealed the presence of α -fetoprotein (AFP) in the cells located in the areas of transitional cell proliferation, but not in the cells of hyperplastic nodules. Most of the AFP-positive cells were poorly differentiated, small, basophilic cells that often formed glandlike structures. The most highly differentiated AFP-positive cells had the morphology of hepatocytes. (26 refs.)

77-7110 Hepatic-Cell Adenoma Presenting with Intraperitoneal Haemorrhage in the Puerperium. (Eng) Hayes, D. (Dept. Histopathology, Belfast City Hosp., Belfast BT9 7AD, Ireland); Lamki, H.; Hunter, I. W. *Br Med J* 2(6099): 1394; 1977.

A 26-yr-old woman died of ip hemorrhage due to rupture of a hepatic cell adenoma 5 days after undergoing caesarean section for her fourth pregnancy. She had a 3.5-yr history of oral contraceptive usage, and her pregnancy began 3 mo after its cessation. Although rupture 13 mo after stopping oral contraceptives is rare, pregnancy may have stimulated active cel-

lular growth in the adenoma, predisposing it to rupture. (5 refs.)

77-7111 Limitation of the Potentialities of Nephroblastoma Differentiation In Vitro. (Eng) Rousseau-Merck, M. F. (Groupe de Pathologie Pédiatrique, INSERM U 77, Hopital Necker Enfants Malades, 149, rue de Sevres, 75730 Paris, Cedex 15, France); Lombard, M. N.; Nezelof, C.; Mouly, H. *Eur J Cancer* 13(2): 163-170; 1977.

The capacity of 15 human nephroblastomas to differentiate in vitro was studied. Chick and mouse embryonic tissues were used as inducers. Cultivation of the nephroblastomas with inducing tissues improved the growth and survival of the explants in six cases and favored in three a quantitative increase in the number of tubules, provided these structures were present in the tumor in situ. No change was observed in nine tumors. (24 refs.)

77-7112 Increased Incidence of Renal Cell Carcinoma with Hypertension. (Eng) Melman, A. (Dept. Urology, Indiana Univ. Medical Center, 1100 W. Michigan St., Indianapolis, IN 46202); Grim, C. E.; Weinberger, M. H. *J Urol* 118(4): 531-532; 1977.

Of 276 patients evaluated for hypertension, a 52-yr-old woman and a 47-yr-old man with 3.5- and 10-yr histories of hypertension, respectively, were found to have renal cell carcinoma. This incidence (0.73%) was 16 times that expected for an age-matched population. Both patients had elevated plasma renin values before nephrectomy, but they remained hypertensive postoperatively. The explanation for this association is unknown. (11 refs.)

77-7113 Breast Cancer in Families. (Eng) Anderson, D. E. (Dept. Biology, Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030). *Cancer [Suppl]* 40(4): 1855-1860; 1977.

In a study of 489 breast cancer pedigrees, the age at diagnosis and bilaterality rate in 887 patients with different familial patterns of the disease was compared with 5,100 unselected patients; and the lifetime probabilities of breast cancer development were estimated in 983 daughters of familial patients. Higher rates of bilaterality and younger age at diagnosis were found in familial as compared to unselected patients. Bilaterality rates were highest in young patients. Familial bilateral patients developed their first primaries about 5 yr earlier than unilateral patients. A 23% lifetime probability of breast can-

cer development was calculated for daughters of patients with any type of family history of the disease. Daughters of patients whose mothers were affected had the highest probability (27%); this group was considered susceptible to a hereditary type of breast cancer, distinct from types involving associated neoplasms and characterized by the occurrence of multiple neoplasms. (24 refs.)

- 77-7114 **Pathogenesis of Pleural Effusion in Carcinoma of the Breast.** (Eng) Weichselbaum, R. (Joint Center Radiation Therapy, 50 Binney St., Boston, MA 02115); Marck, A.; Hellman, S. *Int J Radiat Oncol Biol Phys* 2(9/10): 963-965; 1977.

A total of 352 breast cancer patients treated with postoperative radiotherapy were analyzed for laterality and incidence of pleural effusions. Twenty-five patients developed pleural effusions, 21 ipsilateral and 4 contralateral. The frequency of ipsilateral effusions was significantly greater in patients with chest wall recurrences (6/18) than in those without recurrences (15/334). It is suggested that the effusions arose secondarily to local chest wall involvement and regional spread to the pleura via the chest wall lymphatics. (6 refs.)

- 77-7115 **Microglandular Hyperplasia of the Endocervix Following Long-Term Estrogen Treatment.** (Eng) Tsukada, Y. (Dept. Pathology, Roswell Park Memorial Inst., Buffalo, NY 14263); Piver, M. S.; Barlow, J. J. *Am J Obstet Gynecol* 127(8): 888-889; 1977.

The case report of a 61-yr-old woman who developed microglandular hyperplasia after long-term (11 yr) treatment with Premarin (1.25 mg conjugated estrogens/day) is given. The lesion was originally thought to be an adenocarcinoma, but upon further examination the correct diagnosis was made. Factors responsible for this erroneous diagnosis are discussed. (2 refs.)

- 77-7116 **Ultrastructure of the Uterine Epithelium of Mice Treated Neonatally with Estrogen.** (Eng.) Mori, T. (Zoological Inst., Faculty Science, Univ. Tokyo, Bunkyo-ku, Tokyo 113, Japan). *Acta Anat (Basel)* 99(4): 462-468; 1977.

The ultrastructural changes in the uterine epithelium of 20 C57 Black/Tw mice who had been treated with estrogen (20 μ g daily sc doses of 17 β -estradiol dissolved in 0.02 ml sesame oil) for 10 days, beginning on the day of birth, were investigated. All mice were ovariectomized at 2 mo of age, and divided into groups of five mice. Two of these groups were sacrificed at 3 and 13 mo of age, respectively. The remaining groups

were given a single injection of 10 μ g estradiol in 0.1 ml oil at 3 and 13 mo, respectively, and killed 48 hr later. Mice killed 48 hr after estradiol injection at 3 mo had tall columnar and pseudostratified uterine epithelium. The cisternae of the endoplasmic reticulum was markedly dilated on some of these cells. The nucleus was increased in size and mitochondria were increased both in size and number. The Golgi apparatus was well developed. The uterine epithelium of 13-mo-old mice killed 48 hr after estradiol injection was similar. At 1 mo after ovariectomy, the epithelium of estrogenized mice was composed of columnar and pseudostratified cells. The luminal surface was fuzzy and the rough endoplasmic reticulum was well developed; mitochondria were abundant. In 13-mo-old ovariectomized mice, the epithelium consisted of some columnar cells but was basically stratified and squamous. Spherical basal cells, similar to those in cancerous vagina of estrogen-treated mice, were noted; these cells had the capacity for autonomous proliferation. The mechanism that induced the epithelial stratification is unknown. (17 refs.)

- 77-7117 **Canine Transmissible Venereal Sarcoma: Electron Microscopic Changes with Time after Transplantation.** (Eng) Kennedy, J. R. (Dept. Zoology, Univ. Tennessee, Knoxville, TN 37916); Yang, T. J.; Allen, P. L. *Br J Cancer* 36(3): 375-385; 1977.

The structure of canine transmissible venereal sarcoma (CTVS) was examined from 14 to 71 days after implantation. During early growth, the tumor is composed primarily of loosely arranged, round cells and a few fibroblast-like cells. As the tumor mass increases, the round cells become tightly packed with highly interdigitating plasma membranes. The number of irregularly shaped round cells and fibroblast-like cells increases with increasing tumor mass. Collagen and reticular fibers are found in early tumors, frequently in association with the round cells and in regions devoid of fibroblast-like cells. During tumor regression, cellular degradation is evident in the fibroblast-like, irregularly shaped cells and in the round cells. The data suggest that transformation may occur during tumor growth, causing morphological change from round to fibroblast-like cells, and that CTVS is an undifferentiated round cell sarcoma capable of differentiation in a fibroblastic direction. Also present primarily in tumor cells from newborn dogs, were cytoplasmic lamellar arrays and crystalline viruslike structures, both previously described in other forms of tumor cells. (24 refs.)

- 77-7118 **Ultrastructural Studies on the Effect of Testosterone, 5 α -Dihydrotestosterone, and 5 α -Androstane-3 α ,17 α -diol on the Canine Prostate Cultured In Vitro.** (Eng.) Sinowatz, F. (Tenovus Inst. Cancer Res., Welsh Natl. Sch. Medicine, Health Park,

ardiff, CF4 4XX, Wales) Chandler, J. A.; Pierrepont, G. *J Ultrastruct Res* 60(1): 1-11; 1977.

trastructural examination was made of the effects of testosterone (T), 5 α -dihydrotestosterone (DHT) and 5 α -androstan-3 α ,17 α -diol (AD) at concentrations of 10⁻⁷ to 10⁻⁵ M on organ cultures of canine prostate grown in defined medium. AD maintained the functional polarity of secretory processes of the epithelial cells, but regenerative changes occurred progressively in the presence of T or DHT. Prolonged culture with AD produced stimulation of basal cell growth with consequent hyperplasia. The observations are consistent with AD being the principal active androgen in dog prostate. (37 refs.)

77-7119 **Multicellular Origin of Parathyroid "Adenomas"**. (Eng.) Fialkow, P. J. (Medical Service, Veterans Admin. Hosp., 4435 Beacon Ave. South, Seattle, WA 98108); Jackson, C. E.; Block, M. A.; Greenawald, K. *N Engl J Med* 297(13): 696-698; 1977.

The origin of parathyroid adenomas was investigated in three black women (49 to 57 yr old) with primary hyperparathyroidism who were heterozygous for glucose-6-phosphate dehydrogenase (G-6-PD), an X-linked isoenzyme. Two women had involvement of a single gland, fulfilling the criteria for an adenoma, while the other had involvement of two glands, suggesting chief cell hyperplasia; hypercalcemia resolved in all patients after surgery. Analysis of G-6-PD indicated that both the A and B isoenzymes were present in every adenoma in similar proportions to those observed in the surrounding tissues. Since only one isoenzyme would be present with single cell involvement, these findings suggest a multicellular origin, perhaps as a result of some stimuli, and contradict the clonal theory of origin of parathyroid adenomas. Parathyroid adenomas and hyperplasias may thus be similar biologically as well as pathologically. (19 refs.)

77-7120 **Incidence of Prolactin-producing Adenomas**. (Eng) Horvath, E. (Dept. Pathology, St. Michael's Hosp., Univ. Toronto, Toronto, Ontario, Canada); Kovacs, K.; Ryan, N.; Singer, W.; Ezrin, C. *IRCS Med Sci: Cancer* 5(9): 447; 1977.

Immunoreactive prolactin was demonstrated in the cytoplasm of 6/45 pituitary adenomas found incidentally at autopsy in patients with no manifest pituitary abnormalities. A study of 133 surgically removed pituitary adenomas revealed that 47 were prolactin-producing. Radioimmunoassay revealed raised prolactin concentrations in the blood of 25% to 73% of patients with hypophysial neoplasms. Thus, a variety of pituitary tumors can produce prolactin, and prolactin-producing adenomas are common among pituitary tumors. (8 refs.)

77-7121 **Hematopathology and Pathogenesis of the X-linked Recessive Lymphoproliferative Syndrome**. (Eng) Purtilo, D. T. (Dept. Pathology, Univ. Massachusetts Medical Sch., 55 Lake Ave. N. Worcester, MA 01605); Yang, J. P.; Allegra, S.; DeFlorio, D.; Hutt, L. M.; Soltani, M.; Vawter, G. *Am J Med* 62(2): 225-233; 1977.

The occurrence of the X-linked recessive lymphoproliferative syndrome in six male cousins and, possibly, another boy is reported. Three brothers died of an infectious mononucleosis syndrome; a maternal cousin developed agammaglobulinemia 3-yr after infectious mononucleosis; and two half-brothers of the kindred died of lymphoma of the brain and intestinal tract, respectively. Three of the boys had developed unusual measles viral infections. Paramyxoviruslike particles suggestive of measles virus were seen at necropsy in the atrophic lymphoid tissue of two boys. Also, plasma cells were numerous in the brains, visceral organs, and thymus glands, and T lymphocytes were sparse in the lymph nodes and spleen. The abnormal lymphopoiesis in the syndrome probably results from a subtle immunodeficiency and concurrent measles and Epstein-Barr virus infections. (34 refs.)

77-7122 **Ultrastructure of Myeloma Cells in a Case with Crystalcryoglobulinemia**. (Eng) Kalderon, A. E. (Dept. Pathology, Univ. Arkansas Medical Sciences, 4301 W. Markham, Little Rock, AR 72201); Bogaars, H. A.; Diamond, I.; Cummings, F. J.; Kaplan, S. R.; Calabresi, P. *Cancer* 39(4): 1475-1481; 1977.

The bone marrow of a 53-yr-old man with multiple myeloma associated with spontaneously crystallizing cryoglobulin of the IgG₁ kappa type was studied by electron microscopy. Ultrastructurally, crystalline material was present in the cytoplasm within the rough endoplasmic reticulum (RER), as well as in the extracisternal sites. The crystalline material was also seen extracellularly, and it had a distinctly unique subunit structure. The tubular units measured 200A externally, with an internal diameter of 100A. The intracellular distribution did not indicate a characteristic organelle association usually observed in protein-synthesizing cells. It is suggested that the crystalline material may represent polymerized protein synthesized by free ribosomes mostly in extracisternal locations, a pattern often seen in neoplastic plasma cells. Diffusion of precrystalline material to extracisternal sites through the RER membranes is a possible alternative mechanism. (20 refs.)

77-7123 **Evolution of Reactive Lymphadenopathy into Lymphoma over a Nine-Year Period: A Clinicopathologic Study**. (Eng) Hyland, C. H. (Dept. Pathology, Div. Surgical Pathology, Univ. Alabama, Univ. Station, Birmingham, AL 35294); Murad, T. M.; Dismukes, W. E. *Am J Clin Pathol* 68(5): 606-610; 1977.

A case of lymphoma that was preceded for 9 yr by an apparently reactive lymphadenopathy is reported. The original slides of the multiple lymphoid tissue samples are reviewed, with emphasis on the gradually increasing numbers of mitoses, atypical histiocytes, and eosinophils, features suggestive of malignant transformation. Ultrastructurally, the lymphoma resembled the lymphocyte-depletion variant of Hodgkin's disease. (6 refs.)

- 77-7124 **The Ultrastructure of a Porcine Hereditary Lymphoma with Some Observations on Cell Cultures and Enzyme Cytochemistry.** (Eng.) Campbell, J. G. (De Quincey Cottage, Polton, Lasswade, Midlothian, Scotland). *J Pathol* 122(4): 191-200; 1977.

Ultrastructural studies were performed on affected tissues and cell cultures established from a hereditary lymphosarcoma of Large White pigs. Certain hydrolytic and lysosomal enzymes (the acid and alkaline phosphatases) in tumor cells and cell cultures were also investigated. Examination of the prominently involved mesenteric lymph nodes from older animals revealed a mixed cell population consisting mainly of macrophages, a scattering of lymphocytes, and small clusters of relatively undifferentiated tumor cells. Eosinophils and plasma cells were fairly common. In younger pigs, the affected nodes showed the bulk of the cells to be lymphocytes exhibiting varying degrees of activation and blastoid tumor cells distributed within a mass of reticulum cells. Macrophages were numerous, but eosinophils were less frequent, being more evident in older pigs. Cells seen in well-established culture were predominantly macrophages, with a minority of phagocytic myeloid cells (promyelocytes and/or myelocytes). Nearly all tumors were considered to be poorly differentiated lymphocytic lymphosarcomas, with one possibly classified as a histiocytic; ie, macrophage lymphoma. On rare occasions, particles resembling C-type virus were seen some cells. (19 refs.)

- 77-7125 **Invasion of Lymphosarcoma Cells into the Perfused Mouse Liver.** (Eng) Roos, E. (Div. Cell Biology, Antoni van Leeuwenhoekhuis, Netherlands Cancer Inst., Sarphatistraat 108, Amsterdam, Netherlands); Dingemans, K. P.; van de Pavert, I. V.; van den Bergh-Weerman, M. *J Natl Cancer Inst* 58(2): 399-407; 1977.

The livers of (C57BL x DBA)_F female mice were perfused in situ with a synthetic Hb-free synthetic medium to which approx 10^7 syngeneic lymphosarcoma cells in ascites form (MB VI A) were added. Changes in liver morphology were studied by electron microscopy. Tumor cells passed through the liver. All cells were located in the sinusoids, except for a small number found floating freely in a large vessel. There was no adherence to the endothelium of larger vessels. The cells remained isolated

and were homogeneously distributed over periportal areas. Many lymphosarcoma cells protruded into the endothelial cells, so that several protrusions usually extended into invaginations of the endothelial cell surfaces. Most protrusions extended through openings of the endothelial cells and into the space of Disse. Several also invaded underlying hepatocytes, and some tumor cells migrated out of the sinusoids. In experiments lasting > 90 min, the total percentage of cells that were penetrating or had penetrated the endothelium was constant and reproducible (68%), but the percentage of these cells that also invaded hepatocytes varied widely. In parallel in vivo experiments, invasion of the liver in intact mice was essentially the same as invasion of the perfused liver, although the number of invaded hepatocytes was lower. In addition, the endothelium was disrupted more frequently and to a greater degree. A possible mechanism of tumor invasion, the "endocytosis" of tumor cell processes by cells of the target organ, is suggested. (13 refs.)

- 77-7126 **Chronic Granulocytic Leukaemia Developing upon a Follicular Lymphoma.** (Eng) Erskine, J. G. (Dept. Haematology, Victoria Infirmary, Glasgow G42 9TY, Scotland); Wang, I.; Hutton, M. M. *Br Med J* 2(6098): 1329; 1977.

A 61-yr-old man developed chronic granulocytic leukemia 4 yr after non-Hodgkin's follicular lymphoma. He had been treated with cyclophosphamide (50 mg/day po) for 3 yr. It is suggested that the second neoplasm developed as a result of the alkylating agent therapy. (5 refs.)

- 77-7127 **Chromosome Mapping of the Genes That Control Differentiation and Malignancy in Myeloid Leukemic Cells.** (Eng) Azumi, J. I. (Dept. Genetics, Weizmann Inst., Science, Rehovot, Israel); Sachs, L. *Proc Natl Acad Sci USA* 74(1): 253-257; 1977.

Chromosome banding patterns were analyzed in clones of mouse myeloid leukemic cells that differ in their ability to be induced to undergo normal cell differentiation by the protein inducer MGI (macrophage and granulocyte inducer). The clones were either MGI+ (can be induced to form Fc and C3 rosettes), a stage in the differentiation of myeloid cells, or MGI- (cannot be induced to form these rosettes). All six clones of MGI- cells derived from six independently produced myeloid leukemias had a piece missing from one chromosome 2; this abnormality was not found in MGI+ myeloid leukemic clones or lymphoid leukemias. Five MGI+ mutants, derived from an MGI- clone with an abnormal chromosome 2, one normal chromosome 12, and two translocated chromosomes 12, still had this piece missing in one chromosome 2, but had also lost either the one normal or one of the translocated chromosomes 12. These results indicate that genes controlling the inducibility of sheep RBC coated with antibody (EA) or sheep RBC coated with anti-

body and complement (EAC) rosettes by MGI are located on chromosomes 2 and 12. Data from the mutants suggest that there are suppressor gene(s) on chromosome 12 that can suppress the inducing gene(s) on chromosome 2 and that inducibility by MGI is controlled by the balance between these genes. The loss of a piece of chromosome 2 in MGI cells was present in myeloid leukemic cells before culture and in leukemias produced in vivo from cultured cells. In addition to the changes in chromosomes 2 and 12, there were also abnormalities in chromosomes X and 15 in the various leukemias examined, suggesting that all these chromosomes (2,12,15, and X) may carry genes that control malignancy. (36 refs.)

77-7128 The Philadelphia Chromosome in Human Macrophages. (Eng) Golde, D. W. (Div. Hematology-Oncology, Dept. Medicine, Univ. California at Los Angeles Sch. Medicine, Los Angeles, CA 90024); Burgaleta, C.; Sparkes, R. S.; Cline, M. J. *Blood* 49(3): 367-370; 1977.

Three patients in different phases of chronic myelocytic leukemia were studied. Their bone marrow cells were cultured under conditions favoring macrophage proliferation, and parallel cytogenetic and cytochemical studies were performed. All cell metaphases examined contained the Philadelphia (Ph¹) chromosome at a time when 80% of these metaphases were in identifiable macrophages. It is concluded that the mononuclear phagocyte cell line contains the abnormal chromosome in Ph¹-positive chronic myelocytic leukemia. (17 refs.)

77-7129 Chromosomes and Causation of Human Cancer and Leukemia. XXV. Significance of the Ph¹ Including Unusual Translocations in Various Acute Leukemias. (Eng) Oshimura, M. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263); Sandberg, A. A. *Cancer* 40(3): 1149-1160; 1977.

The results of studies on three patients with Ph¹-positive acute leukemias are presented. A 34-yr-old woman with acute lymphoblastic leukemia (ALL) in relapse had a hypodiploid karyotype, primarily 43,-X,-7,-8,9p+. Subsequent complete remission with a normal chromosomal picture was followed by the appearance of cells with a 46,XX,Ph¹ karyotype. The Ph¹ was due to a standard translocation between chromosomes number 9 and 22. A 39-yr-old man with acute myeloblastic leukemia (AML) had a translocation between the long arm of number 22 and number 19; other chromosomal markers included a loss of the short arms of numbers 7 and 9. In a 66-yr-old woman with erythroleukemia, the modal chromosome number was 45; she had a translocation between chromosomes 4 and 22. Two clones were present, one in which the Ph¹ was the only abnormality and one which had missing number 7 chromosome in addition to the Ph¹. The patient with ALL had null cell type leukemia and the ALL specific antigen. The patient with AML was also null cell but was negative for the antigen. It is suggested that the presence

of normal karyotypes in Ph¹-positive leukemia is indicative of acute disease per se and not of the blastic phase of chronic myelocytic leukemia. (37 refs.)

77-7130 Chromosome Studies of the Transplantable Shay Chloroleukemia in Rats. (Eng) Atl, B. (Box 420, Univ. Chicago Hosps. and Clinics, 950 E. 59th St., Chicago, IL 60637). *J Natl Cancer Inst* 58(5): 1437-1442; 1977.

Chromosomes from tumors in male Long-Evans rats with transplantable Shay chloroleukemia were counted and analyzed by Giemsa staining and quinacrine fluorescence. Several consistent abnormalities were noted in 43 metaphase cells. An interstitial deletion of the distal portion of chromosome 2 was present in all 43 cells. Trisomy for No. 2 was found in 27 metaphases; the third No. 2 had a terminal deletion, resulting in a chromosome shorter than the other deleted No. 2. All cells were missing chromosome 11, but most contained a large acrocentric chromosome that appeared to be a No. 10 with a terminal addition (10q+). Several markers were also noted consistently. This study corroborates previous reports of the specificity of chromosome 2 in chemically induced tumors and supports the concept that this chromosome may be important in oncogenesis in the rat and in the host response to different etiologic agents. (28 refs.)

77-7131 Chronic Lymphocytic Leukemia with Cytoplasmic Inclusions. (Spa) Julia, A. (Servicio de Hematología y Hemoterapia, Ciudad Sanitaria 'Francisco Franco', Barcelona, Spain); Irriguible, M. D.; Woessner, S. *Sangre (Barc)* 22(2): 235-242; 1977.

A case of chronic lymphoproliferative disease characterized by the presence of cytoplasmic inclusions similar to Russell's bodies occurred in a 39-yr-old woman. There was a high percentage of lymphocytes from the patient's peripheral blood, bone marrow, and lymph nodes since the time of onset of the disease and through the 6-yr duration and follow-up. The inclusions were studied by light and electron microscopy and cytochemistry. They were round or oval and usually distributed, singly or in clusters, throughout the cytoplasm, but occasionally they were displaced peripherally to the nucleus. They were devoid of β -glucuronidase and acid phosphatase activity, and they gave a negative result in the peroxidase test and a positive PAS reaction. The lymphocytes had an increased number of ribosomes, most of which were clustered around the inclusions. Although intracellular immunoglobulins (Ig) were not detected, the lymphocytes may have an increased synthesis of Ig that are not adequately secreted, perhaps because of the scarcity of the rough endoplasmic reticulum. These Ig may accumulate in the cytoplasm, forming the inclusions described. (21 refs.)

77-7132 Hairy Cell Leukemia: A B-Cell Neoplasia. (Spa) Burgaleta, C. (Servicio de Hematología, Centro

de Especialidades Medico Quirurgicas 'Ramon y Cajal,' Madrid, Spain); Golde, D. W. *Sangre (Barc)* 22(2): 148-158; 1977.

Lymphocytes from 20 patients with hairy cell leukemia (leukemic reticuloendotheliosis) were studied by cytochemistry, immunofluorescence, and electron microscopy. Increased tartrate-resistant acid phosphatase activity was a characteristic finding in these cells. Surface receptors for immunoglobulins and complement were demonstrated by antibody and antibody-complement rosette formation. Membrane and cytoplasmic immunoglobulins were detected in the two patients studied. The neoplastic nature of the disease was demonstrated by the inability of the lymphocytes to mature in liquid culture. Moreover, the cells had no colony-stimulating activity in liquid or semisolid gel culture. Transmission electron microscopy revealed microvilli and abundant mitochondria and the ribosome-lamella complex in these hairy cells. Scanning electron microscopy demonstrated the presence of ruffles and microvilli on the cell surface. It is suggested that leukemic reticuloendotheliosis is a neoplastic disorder of B lymphocytes with a clonal origin. (42 refs.)

- 77-7133 **Kinetic Studies of a Tumor-induced Leukemoid Reaction in Mice.** (Eng) Boggs, D. R. (Univ. Pittsburgh Sch. Medicine, 931 Scaife Hall, Pittsburgh, PA 15261); Malloy, E.; Boggs, S. S.; Chervenick, P. A.; Lee, R. E. *J Lab Clin Med* 89(1): 80-92; 1977.

CE mice were inoculated sc with 0.2 ml of a crude transplantable breast tumor homogenate, and kinetic studies were performed. The tumors were palpable within 1 wk and usually fatal by 4 wk, unless removed. There was an initial decrease in blood WBC followed by a rapid increase that peaked at av levels of 165,000/mm³ by day 18. This increase held for all WBC, but the largest increase was in neutrophils. Total nucleated cells per humerus declined initially, returned to control levels, and again declined after 10 days posttransplant. However, the percentage of cells that were peroxidase-positive increased initially until a plateau at 150% of control values was reached; they then declined gradually toward control levels. Nucleated RBC and lymphocytes declined. The thymidine labeling index of neutrophil-producing cells was not significantly different from that of controls; the emergence of blood neutrophils was also normal, but the decline in labeled cells was slow in tumor-bearing mice. A marked increase in erythropoiesis was observed in the spleens of tumor-bearing mice, but total erythropoiesis appeared normal. The number of progenitor granulocytic and mononuclear cells decreased in the marrow during tumor growth. Colony-forming cells declined during the first week and remained at approx 50% control levels for 3 wk. Colony-stimulating activity in plasma was slightly increased during the early phase of tumor growth and decreased during later phases. Surgical removal of the tumor resulted in reversal of the leukemoid reaction. These findings suggest that the leukemoid reaction is due to an increased blood transit time of the neutrophils. (28 refs.)

- 77-7134 **Biochemical Characterization of the Tartrate-resistant Acid Phosphatase of Human Spleen with Leukemic Reticuloendotheliosis as a Pyrophosphatase.** (Eng) Lam, K. W. (Dept. Ophthalmology, Albany Medical Coll. Union Univ., Albany, NY 12208); Yam, L. T. *Clin Chem* 23(1): 89-94; 1977.

The biochemical properties of a tartrate-resistant acid phosphatase isolated from the spleen of a patient with leukemic reticuloendotheliosis were determined. Carboxymethyl cellulose chromatography of the enzyme revealed four major peaks, with the highest enzyme activity in peak I (fraction 25). The purified enzyme was stable if stored below 0°C; only 20% of the activity was lost after the enzyme remained at room temperature for 20 hr, but about 90% of the activity was lost when it was kept at 80°C for 30 min. The mol wt of the enzyme corresponded to about 64,000 daltons. The purified enzyme had similar catalytic activity for organic and inorganic pyrophosphates and was active on monophosphoesters of phenolic compounds. No detectable activity was observed for AMP, glucose-6-phosphate, fructose-1,6-diphosphate, α -glycerol phosphate and β -glycerol phosphate, phosphoserine, pyridoxal phosphate, and phosphamide. Optimal activity was observed between pH 5 and 6 when ATP or p-nitrophenylphosphate was the substrate. The enzyme was unaffected by 1 to 5 mM ascorbate or 0.1 μ M p-chloromercuriphenylsulfonate. It was inhibited by FeSO₄, ZnSO₄, MgSO₄ (1 mM) and o-phenanthroline (50 and 150 mM) and was extremely sensitive to 0.1 μ M molybdate. (25 refs.)

- 77-7135 **Systemic Mastocytosis in a Patient with Polycythemia Vera Treated with Radioactive Phosphorus.** (Eng) Eagan, J. W. (Dept. Pathology, Johns Hopkins Hosp., Baltimore, MD 21205); Baughman, K. L.; Miller, S.; Conley, C. L.; Eggleston, J. C. *Blood* 49(4): 563-571; 1977.

A 49-yr-old man died of systemic mastocytosis after a 21-yr treatment of polycythemia vera with ³²P. This case may represent proliferation of a line of hyperstimulated primitive mesenchyme as a result of the radiation and/or the disease. (24 refs.)

- 77-7136 **Relationship Between Transcerebral Passage of Tumor Cells and Brain Metastasis.** (Eng) Kawaguchi, T. (Second Dept. Pathology, Fukushima Medical Coll., 5-75 Sugitsuma-cho, Fukushima 960, Japan); Nakamura, K. *Gann* 68(1): 65-71; 1977.

The relationship between the transcerebral passage of tumor cells and brain metastases was examined in female Donryu rats inoculated in the right carotid artery with cells of seven ascites hepatomas, including the Yoshida sarcoma. Tumor strains with relatively low transcerebral passage rates (AH-

130, AH-272, and AH-7974) resulted in more frequent metastatic foci in the brain parenchyma than strains with comparatively high passage rates (Yoshida sarcoma, AH-7974F, AH-66F, and AH-13). Thus, the incidence of brain metastasis correlated with transcerebral passage rates. The mechanisms of metastasis formation are discussed with special reference to the arrest of tumor cells in blood vessels. (24 refs.)

77-7137 Excess Chromosome #4 in Ethylnitrosourea-induced Neurogenic Tumor Lines of the Rat. (Eng) Au, W. (Section Cell Biology, Univ. Texas System Cancer Center, Houston, TX 77030); Soukup, S. W.; Mandylbur, T. I. *J Natl Cancer Inst* 59(6): 1709-1716; 1977.

The chromosomes in 15 cell lines derived from separate tumors induced in Sprague-Dawley rats by ethylnitrosourea (ENU) are described. Thirteen lines were neural (glioma or schwannoma) in origin and type. In 12 of these lines, excess chromosome #4 was demonstrated by Giemsa banding. One to three extra #4 chromosomes were seen as numerical or structural abnormalities. Also noted were other changes that were not consistent among the lines. The 12 lines produced tumors in newborn rats. The 13th neurogenic line lacked excess chromosome #4 and did not produce tumors. The remaining two lines were nonneurogenic and lacked excess chromosome #4, but they produced tumors. Control studies included chromosome analyses of bone marrow preparations from ENU-treated rats with tumors, cell lines from brains of normal rat embryos, and two established nonneurogenic rat tumor lines. No excess chromosome #4 was seen. These results suggest that nondisjunction and/or rearrangement of chromosome #4 is associated with the oncogenic process in neurogenic tumors induced by ENU. (30 refs.)

77-7138 Changes of Somatic Cell Chromosomes in Precancerous and Cancerous Transformation of Irradiated Tissue. (Rus) Strel'tsova, V. N. (No affiliation given); Strashnenko, S. I.; Zhukova, I. V. *Vopr Onkol* 23(9): 86-87; 1977.

Changes in the karyotype and cellular composition of the hematopoietic system were studied in female CC57Br mice following administration of tritium oxide (0.5 mCi/g ip). Bone marrow hypocellularity and chromatid and chromosome mutations occurred in 27%-47% of the cells during the first month. Solitary symmetrical translocations were found in all animals on day 14. There were no other changes until days 210-270, when cellular and karyotypic polymorphism was observed. Depression of erythropoiesis, a slight increase in reticulocyte count, absence of unstable chromosome aberrations, and a highly significant rise in the percentage of cells with marker chromosomes were seen in 4/37 animals. A prevalence of promyelocytes and myelocytes was observed in 18/37 animals; 23% of them showed chromosome defects, 6.5% translocations, and 3.3% unstable aberrations (breaks, deletions). Erythropoiesis was depressed in mice with preleu-

kemia and leukemia; the karyotype of the myeloid cells showed that the number of cells with marker chromosomes (13%-36%) was two to three times as high as that in mice with other hematopoietic diseases. The percentage of aneuploid cells was 5%-8%. No cells with marker chromosomes and 5.3% damaged cells were seen in the control group. The findings indicate a parallelism between the preleukemic and leukemic states and the accumulation of cells with telocentric translocations in the bone marrow. (no refs.)

77-7139 Chromosome Complement and SV40 Transformation of Cells from Patients Susceptible to Malignant Disease. (Eng) Webb, T. (Dept. Cancer Studies, Univ. Birmingham, Medical Sch., Birmingham, B15 2TJ, England); Harding, M. *Br J Cancer* 36(5): 583-591; 1977.

Fibroblasts from patients with differing susceptibilities to malignant disease were compared with respect to their chromosome complements and their transformation with simian virus 40 (SV40). Fibroblasts from two Bloom's syndrome patients did not show increased SV40 transformation rates, and no correlation was found between chromosome abnormality and transformation. Of two cell types with greatly increased rates, one was derived from a neurofibromatosis patient and the other from an A-T heterozygote. When SV40 DNA was employed as the transforming agent for the latter, the transformation rate was no longer raised. (27 refs.)

77-7140 Tumor x Host Cell Hybrids in the Mouse: Chromosomes from the Normal Cell Parent Maintained in Malignant Hybrid Tumors. (Eng) Aviles, D. (Institut de Recherches Scientifiques sur le Cancer du Centre National de la Recherche Scientifique, Boite Postale 8, 94800 Villejuif, France); Jami, J.; Rousset, J. P.; Ritz, E. *J Natl Cancer Inst* 58(5): 1391-1399; 1977.

The relationship between the malignancy of normal cell/malignant cell hybrids and the loss of specific genes borne by specific chromosomes of the normal parent cells was investigated. Tumors produced in mice by the injection of Cl.1D cells (L-cell derivatives) contained tumor x host cell hybrids. Hybrid cell populations isolated from 14 tumors were injected into 123 mice, 108 of which developed tumors. Metaphases of growing hybrid cell tumors were analyzed by a trypsin-Giemsa banding technique. The chromosomes contributed by the host (normal) parent cell could be distinguished from the Cl.1D chromosomes, as the latter exhibited none of the normal cell chromosomes bore genetic information capable of suppressing the malignancy of Cl.1D cells. The absence of complementation in the hybrids suggested that if the malignancy of the Cl.1D cells was caused by mutations at several linked loci, none of the mutations was recessive. (56 refs.)

77-7141 Pathology of Human-Mouse Somatic Cell Hybrid Tumors. (Eng) Aden, D. P. (Wistar Inst. Anatomy and Biology, 36th at Spruce, Philadelphia, PA

19104); Putong, P.; Iwasaki, Y. *J Natl Cancer Inst* 59(4): 1243-1249; 1977.

Tumor lines were established following sc inoculation of C57BL/6J peritoneal macrophages and simian virus 40 trans-morphologic differences due to rearrangements. Although none of the hybrid metaphases had a complete set of chromosomes from the normal cell parent, individual chromosomes were present in most of the 14 hybrid tumors. Therefore, formed Leseh-Nyhan human fibroblasts (LV-SV) into nude mice. The hybrids were a heterogeneous population with 14 different human chromosomes and a quasi-tetraploid number of mouse chromosomes. A fast growing tumor (N9) and a slow growing tumor (N8) were removed on days 22 and 76, respectively, and passaged in vivo in nude mice. After the second in vivo passage, the N9 tumor contained human chromosome 7 in 100% of the cells and chromosome 6 in 70%. The N8 tumor contained only human chromosome 7 in 100% of the cells. In vitro cultures of these tumors were prepared, and resulting cells produced tumors when injected sc into mice. The histology of these tumors is presented. Electron microscopically, both tumors were indistinguishable, consisting of undifferentiated mesenchymal cells; and no virus particles were observed. Repetition of the experiment with BALB/c x LN-SV hybrids produced tumors with similar morphology. These hybrids contained a near diploid mouse chromosome count and only a few human chromosomes. Two clones contained only human chromosome 7 and resembled N9 and N8; a third clone contained human chromosomes 7, 5, and 11 and resembled N9. These findings indicate that human mouse cell hybrids can produce more than one stable tumor type. (6 refs.)

77-7142 **Morphology and Pathogenesis of Tumors of the Thymus and Stomach in Sprague-Dawley Rats Following Intragastric Administration of Methyl Nitrosourea (MNU).** (Eng) Koestner, A. W. (Dept. Pathology, Ohio State Univ., Columbus, OH 43210); Ruecker, F. A.; Koestner, A. *Int J Cancer* 20(3): 418-426; 1977.

The intragastric intubation of N-methyl-N-nitrosourea (MNU) (20 mg/kg twice weekly for 9 wk) into young Sprague-Dawley rats resulted in a 100% incidence of thymic lymphomas and gastric carcinomas in animals surviving more than 14 wk. Progressive thymic atrophy following MNU administration culminated in marked lymphoid depletion by the 5th wk of treatment. At 6 wk, repopulation of the thymus with lymphoblastic cells was observed, followed by thymic neoplasia. The first thymic lymphoma appeared at wk 6. By wk 15 all rats were either moribund or had succumbed to anoxia caused by pleural effusions associated with thymic neoplasia. Twenty six of 31 thymic tumors were classified as lymphocytic lymphomas, 2 as histiocytic, 1 as mixed lymphocytic-histiocytic, 1 as bimorphic, and 1 as an epithelial thymoma. All but two lymphomas were restricted to the thymus. Both of these were histiocytic lymphomas,

one involving the spleen, liver, and abdominal lymph nodes and the other infiltrating locally into cervical and thoracic regions. Significant thymic enlargement occurred only after the end of MNU treatment at 9 wk, which indicated that MNU had also acted as a chemotherapeutic agent. The gastric carcinomas were restricted to the nonglandular portion of the stomach, and they developed as a final step following ulceration and hyperplasia. The short latency period and the high incidence of thymic neoplasms recommend use of this model for pathomorphogenetic as well as immuno- and chemotherapeutic investigations. (31 refs.)

77-7143 **Decrease in the Incidence of Malignant Ileocaecal Immunocytoma in LOU/c Rats after Surgical Removal of the Ileocaecal Lymph Nodes.** (Eng.) Moriame, M. (Experimental Immunology Unit, Faculty Medicine, Univ. Louvain, 30 Clos Chapelle-aux-Champs, 1200 Brussels, Belgium); Beckers, A.; Bazin, H. *Cancer Lett* 3(3-4): 139-143; 1977.

Malignant ileocecal immunocytomas (MII's) frequently arise spontaneously in LOU/c/Wsl rats. However, excision of the ileocecal lymph nodes significantly reduced tumor incidence, suggesting that the primary cells undergoing malignant transformation are in the ileocecal nodes. After 8 mo, 159/503 control rats had MII's, compared to 1/60 rats that had undergone total ileocecal lymphadenectomy before weaning and 0/61 rats that had a total ileocecal and mesenteric lymphadenectomy between 2 and 3 mo of age. Of the 80 adult animals that had undergone a limited ileocecal lymphadenectomy between 2 and 3 mo of age, 5 have had MII's so far (experiment still in progress). (10 refs.)

77-7144 **Establishment and Characteristics of Three Mouse Cell Lines from Embryos of Different Inbred Strains.** (Eng) Miyazawa, T. (Aichi Cancer Center Res. Inst., Kanokoden Tashiro-cho, Chikusa-ku, Nagoya 464, Japan); Umeda, M. *Gann* 68(1): 37-43; 1977.

Cell lines Y-DD, Y-AK, and Y-Ch were established from DDD, AKR, and C3H mouse embryos, respectively, and characterized. After an initial period of rapid proliferation, the growth rates of the lines declined for 30 to 40 days and rose again for 70 days. After this time, the cell acquired the capacity to grow indefinitely. The growth rate of Y-AK remained unchanged through the 59th generation; that of the others increased with subculture. The saturation density of Y-DD increased with successive transfers, but that of the other two lines remained fairly constant. All lines were either diploid or tetraploid when they became established (17th or 18th generation). By the 40th generation, the chromosome number of Y-DD was hypertetraploid and the other two were in the tetraploid range. In transformation experiments, Y-DD cells exposed to 0.25-0.5 μ g/ml 7,12-dimethylbenz(a)anthracene (DMBA) formed 37.0 and

41.0 transformed foci/dish; exposure to 4×10^{-8} M 4-nitroquinoline 1-oxide (4-NQO) resulted in 10 foci/dish. When no carcinogen was added, 8.5 foci/dish were noted. Y-AK cells formed 0.25 focus when exposed to 0.05 $\mu\text{g/ml}$ DMBA and 1.5 foci with 1.0 $\mu\text{g/ml}$ N-methyl-N'-nitro-N-nitrosoguanidine. No foci were observed in untreated dishes. Y-CH cells formed 8.5 and 5.5 foci when exposed to 0.05 and 0.1 $\mu\text{g/ml}$ DMBA, respectively, and 5.5 foci with 3×10^{-8} and 4.3 with 1×10^{-7} M 4-NQO. With no carcinogen, 9.5 foci were observed. When tested for their ability to form water-soluble products from benzo(a)pyrene, Y-DD cells (29th generation) formed 700 picomoles (pmol)/ 10^6 cells/24 hr, Y-AK cells (53rd generation) formed 4,100 pmol/ 10^6 cells/24 hr. The association between high metabolic efficiency and sensitivity to carcinogenic hydrocarbons held for all cultures. Exposure of all lines to 0.25 and 0.5 $\mu\text{g/ml}$ DMBA resulted in a 25% kill in Y-DD, 25%-50% damage in Y-AK, and a 50% kill in Y-CH. (19 refs.)

77-7145 Morphology and Serum Dependence of Cloned Cell Lines Undergoing Spontaneous Malignant Transformation in Culture. (Eng) Sanford, K. K. (Lab. Biochemistry, NCI, NIH, USPHS, US Dept. Health, Education, and Welfare, Bethesda, MD 20014); Handleman, S. L.; Jones, G. M. *Cancer Res* 37(3): 821-830; 1977.

Several pairs of nonneoplastic and spontaneously transformed cell lines were isolated from NCTC clones 7914, 7915, 7505, 7988, and 7996 (initiated from C3H/HeN embryo fibroblasts) and characterized. Morphologic changes that correlated with transformation included increased cytoplasmic basophilia, reduced spreading of cells on the substrate, increased nuclear:cytoplasmic ratio, greater heterogeneity in the size and shape of cells and nuclei, and a more random orientation of cells. Because these changes are reproducible, they can serve as a guide for identifying spontaneous transformants among cultured rodent fibroblasts. Some of these clones had a higher transformation frequency than the parental line, which had remained nonneoplastic for years. Thus, capacity for continuous in vitro growth is independent of malignant potential. The addition of horse serum did not accelerate or increase the frequency of neoplastic transformation. (31 refs.)

77-7146 Degradation of Basement Membrane by Murine Tumor Cells. (Eng) Liotta, L. A. (Lab. Pathology, NCI, NIH, Public Health Service, US Dept. Health, Education, and Welfare, Bethesda, MD 20014); Kleinerman, J.; Catanzaro, P.; Rynbrandt, D. *J Natl Cancer Inst* 58(5): 1427-1431; 1977.

Tumor cells from the murine T241 fibrosarcoma, which produces pulmonary metastases rapidly and reproducibly, were tested in vitro for their ability to degrade isolated pulmonary basement membranes. Degradation of the basement mem-

brane substrate was quantified by culture of the substrate with tumor cells and by measurement of the solubilized hydroxyproline and hexose glycoprotein at neutral pH. Tumor cells collected in the tumor venous drainage were associated with a significantly greater solubilization of the basement membrane than were tumor cells from the primary tumor mass. Venous effluent tumor cells also solubilized type I collagen from human dura to a significantly greater extent than primary tumor cells, spleen cells, or liver cells. These findings suggest that metastasizing tumor cells may be a distinct tumor subpopulation with regard to their invasive potential. (31 refs.)

77-7147 Teratocarcinoma Differentiation: Plasminogen Activator Activity Associated with Embryoid Body Formation. (Eng) Linney, E. (Dept. Biochemistry and Biophysics, Univ. California at San Francisco, San Francisco, Ca 94143); Levinson, B. B. *Cell* 10(2): 297-304; 1977.

Changes in plasminogen activator activity were examined in mouse embryonal carcinoma cells aggregated and differentiated into cystic embryoid bodies. The pluripotent embryonal carcinoma cells aggregated within 10 days of their transfer from tissue culture to bacteriological culture. A layer of endodermal cells appeared on the outside of the aggregate, forming an embryoid body; a basement membrane formed between the outer layer of endodermal cells and the internal cells; a cyst formed within the embryoid body; and the internal cells assumed a columnar appearance along the inner portion of the basement membrane. Intracellular plasminogen activator activity rose after formation of the endodermal layer. This rise continued for 25 days, provided that the three-dimensional integrity of the embryoid bodies was maintained. Selective removal of the outer endodermal layer reduced the plasminogen activator activity of the resulting embryoid body cores. The intracellular and secreted plasminogen activator activity of simple embryoid bodies composed of only two cell types could be increased by culturing the embryoid bodies in theophylline, or cholera toxin. These results suggest that the embryoid body endodermal cells are the source of a cyclic AMP-inducible plasminogen activator activity. (32 refs.)

See also:

*(Rev.): 77-6604, 77-6610, 77-6613, 77-6621, 77-6625, 77-6627, 77-6633, 77-6634, 77-6636, 77-6642, 77-6646, 77-6652, 77-6653, 77-6654, 77-6655, 77-6656, 77-6657, 77-6659, 77-6660, 77-6661, 77-6662, 77-6663.

*(Chem.): 77-6669, 77-6673, 77-6710, 77-6711, 77-6713, 77-6732, 77-6734, 77-6738, 77-6762, 77-6773, 77-6785, 77-6792, 77-6794, 77-6805, 77-6827, 77-6841, 77-6849, 77-6855, 77-6856, 77-6857, 77-6863, 77-6864, 77-6866, 77-6867, 77-6876.

*(Phys.): 77-6886, 77-6889, 77-6893, 77-6894, 77-6895, 77-6899, 77-6909.

*(Viral): 77-6974, 77-6990, 77-6995, 77-6997, 77-7015, 77-7019.

*(Immun.): 77-7072, 77-7077.

*(Epid.-Biom.): 77-7149, 77-7150, 77-7151, 77-7152, 77-7169.

- 77-7148 **Patient Interview Study from the Third National Cancer Survey: Overview of Problems and Potentials of These Data.** (Eng) Williams, R. R. (Dept. Internal Medicine, Univ. Utah Coll. Medicine, Salt Lake City, UT 84121); Stegens, N. L.; Horm, J. W. *J Natl Cancer Inst* 58(3): 519-524; 1977.

An interview requesting information on epidemiologic variables was sought for 13,179 cases of invasive cancer, a random 10% sample of the Third National Cancer Survey (TNCS) cases in all areas except Iowa. The nonresponse rate was 43%, but no strong nonresponse bias was found when the 7,518 respondents were compared with all TNCS cases for age, race, sex, marital status, method of diagnosis, vital status, country of birth, and site distribution. There was little or no difference in these variables. In the absence of normal controls, two approaches are suggesting for testing associations between exposure variables such as tobacco and alcohol use, socioeconomic status, and selected chronic diseases and specific cancer sites. These are (1) an intercancer comparison of patients with cancer at one site with those having cancers at other sites in the interview study, and (2) an external comparison of interview patients with subjects of other studies with comparable data. The need for caution with either approach is emphasized. (8 refs.)

- 77-7149 **Family History: A Criterion for Selective Screening.** (Eng) Anderson, D. E. (Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Houston, TX 77030); Romsdahl, M. M. *Prog Cancer Res Ther* 3: 257-262; 1977.

The use of family history of cancer as a criterion for selective screening was examined in relatives of patients with colorectal or breast cancer. The subject had to have at least two relatives with colorectal or breast cancer. Among the 188 colonic examinations (76 men, 112 women), 5 colonic cancers, 1 ovarian adenocarcinoma, and 1 breast carcinoma were detected. The detection rates of 2.7/100 examinations at all ages and 3.7/100 at ages ≥ 35 exceeded those reported in detection programs of the general population (1/1,000). The detection rate was much higher among relatives known to belong to polyposis families. Only 2/5 cancers detected in the colonic cancer families were within the range of the proctosigmoidoscope, indicating that in examinations for familial-occurring colorectal cancer, methods that encompass the entire colon should be used. A total of 102 asymptomatic women (15-79 yr old) whose relatives had breast cancer were examined. Suspicious masses were detected in 10 women, 6 of

whom underwent biopsy. Three were histologically diagnosed as duct cell carcinoma, adenocarcinoma, and lobular carcinoma in situ. The detection rates of 2.8/100 at all ages and 4.2/100 at ages ≥ 35 exceeded those observed in screening programs of the general population. Women with a family history of breast cancer have a three- to fourfold higher risk for the disease than women without a family history. These results indicate the feasibility of using family history of a common cancer as a criterion for defining a risk group. The numbers involved are too small and the follow-up period is too short to determine whether these early detections will lead to increased survival rates. (11 refs.)

- 77-7150 **Familial Cancer Syndromes: A Survey.** (Eng) Lynch, H. T. (Dept. Preventive Medicine/Public Health, Creighton Univ., Omaha, NB 68178); Guirgis, H. A.; Lynch, P. M.; Lynch, J. F.; Harris, R. E. *Cancer [Suppl]* 39(4): 1867-1881; 1977.

Genetic studies of several hereditary precancer syndromes are reviewed. The syndromes include familial malignant melanoma, familial polyposis coli, Cancer Family Syndrome, breast carcinoma, Sipple's syndrome (MEA II), multiple mucosal neuroma syndrome (MEA III), tuberous sclerosis, multiple nevoid basal cell carcinoma syndrome, and von Recklinghausen's neurofibromatosis. Analysis of pedigrees exhibiting these syndromes may provide information concerning a genetic etiology for the familial clustering phenomenon of cancer. The data indicate that several syndromes are inherited as autosomal dominant traits. The familial breast cancer and colon cancer syndromes both show marked heterogenous expression. Biochemical markers, such as serum alkaline phosphatase and calcitonin, have been used in a regimen for screening patients with Sipple's syndrome. In MEA II and MEA III, the tumor source appears to be the parafollicular cell of the thyroid. Further investigations should be focused on specific stages of gene action, such as the neural crest differentiation of embryogenesis. (34 refs.)

- 77-7151 **Management of Hereditary Site-specific Colon Cancer.** (Eng) Lynch, H. T. (Dept. Preventive Medicine, Creighton Univ. Sch. Medicine, 2500 California St., Omaha, NB 68178); Harris, R. E.; Bardawil, W. A.; Lynch, P. M.; Guirgis, H. A.; Swartz, M. J.; Lynch, J. F. *Arch Surg* 112(2): 170-174; 1977.

Vital cancer statistics were collected on 232 individuals of a

family in which 33 members were affected with carcinoma of the colon. The pedigree showed transmission of colon cancer on a site-specific basis through five generations. There was an autosomal dominant inheritance pattern, early onset of cancer with predilection for the right colon, and frequent extraprimary cancers of the colon. Fourteen family members were treated successfully for their initial colon cancer by local resection. In 11 of these patients, subsequent primary malignancies of the remaining colon developed 2-23 yr after surgery. Two brothers who were treated for colon cancer by hemicolectomy and were apparently cancer-free 5 yr after operation underwent prophylactic total colectomy. The resected colon from one of these patients had an occult adenocarcinoma in a villoglandular polyp. This demonstrates the potential for cancer control through knowledge of cancer genetics and syndrome identification. It is concluded that hereditary site-specific colon cancer should be included in the differential diagnosis of familial colon cancer, as exemplified by familial polyposis coli and the Gardner, Turcot, and cancer family syndromes. (10 refs.)

- 77-7152 **A Comparison of Hodgkin's Disease in Alameda County, California, and Connecticut: Histologic Subtype and Age Distribution.** (Eng.) Silverman, D. T. (Biometry Branch, NCI, Bethesda, MD 20014); Correa, P.; O'Connor, G. T.; Myers, M. H.; Axtell, L. M.; Bragg, K. U. *Cancer* 39(4): 1758-1763; 1977.

The histologic patterns of Hodgkin's disease (HD) in Alameda County, California, and Connecticut were compared with respect to age. All HD cases from the Alameda County Cancer Registry diagnosed between 1960 and 1969 were reviewed and histologically subtyped according to the Rye classification (159 cases). The age-specific relative frequencies and incidence rates for the subtypes were estimated and compared with those estimated for HD in Connecticut. The morphologic expression of HD in both areas was similar and characteristic of economically developed regions with high living standards. The comparison supports the hypothesis that the host immune capacity, influenced by socioeconomic factors, has a strong and measurable effect on the pathogenesis of HD. (6 refs.)

- 77-7153 **Clustering and Aggregation of Exposures in Hodgkin's Disease.** (Eng.) Grufferman, S. (Duke Univ. Comprehensive Cancer Center, Box 2914, Duke Univ. Medical Center, Durham, NC 27710). *Cancer [Suppl]* 39(4): 1829-1833; 1977.

Epidemiological evidence for case clustering among patients with Hodgkin's disease (HD) is reviewed. Results of statistical searches for time-space clustering have been inconclusive. Methods of infectious disease epidemiology were used to study aggregation of HD cases at high schools in Nassau and

Suffolk counties on Long Island, New York. The findings imply aggregation of etiologic exposures and communicability of HD. However, the results are also compatible with a hypothesis of common-source exposure to noninfectious etiologic agents. Other studies of physicians and teachers, both with high occupational exposure to HD patients, revealed no evidence of increased risk for HD. Familial aggregations of HD have been reported, but an environmental etiology, especially in sibling pairs, has been suggested. If HD is communicable, it is probably so only prior to manifestation of the disease, and exposure must occur in childhood or adolescence. (33 refs.)

- 77-7154 **Characteristics in Youth Indicative of Adult-Onset Hodgkin's Disease.** (Eng) Paffenbarger, R. S. (California State Dept. Health, 2151 Berkeley Way, Berkeley, CA 94704); Wing, A. L.; Hyde, R. T. *J Natl Cancer Inst* 58(5): 1489-1491; 1977.

College entrance health data of 50,000 men were reviewed in search of support for any hypotheses that Hodgkin's disease (HD) is of infectious origin. Students examined in the years 1916-1950 were followed through 1974, and 45 cases of fatal adult-onset HD were found. The records of these 45 men were compared with those of 180 surviving classmates with reference to certain indicator characteristics. Risk ratios of HD tended to be lower for men who had experienced various common contagious diseases in childhood. This reduced incidence of clinical contagions may signify that: (1) inadequate early challenge of immune mechanisms left subjects more susceptible to later HD; (2) heightened immune mechanisms that led to subclinical attacks of early contagious diseases promoted an autoimmune response that evolved as HD; or (3) early childhood infections eliminated some subjects who otherwise would have attended college and ultimately developed adult-onset HD. HD risk was higher for students who reported an early death of a parent, particularly from cancer. This risk tended to be higher among collegians who were obese, heavy cigarette smokers, and coffee drinkers. This correlation with cigarettes and coffee may be suggestive of endogenous rather than societal or exogenous implications. Along with obesity and early parental death, the indicator characteristics in early youth may reflect other personal influences such as familial environment, genetic tendencies, or altered immune status. The findings provide definitive evidence neither for nor against an infectious origin of adult-onset HD. (15 refs.)

- 77-7155 **Cancer Incidence Following Infectious Mononucleosis.** (Eng) Carter, C. D. (Cancer and Birth Defects Div., Bureau Epidemiology, Center Disease Control, Atlanta, GA 30333); Brown, T. M.; Herbert, J. T.; Heath, C. W. *Am J Epidemiol* 105(1): 30-36; 1977.

The incidence of cancer among 2,282 former college students who developed heterophile-positive infectious mononucleosis (IM) between 1949 and 1969 at five US universities was examined. Cancer incidence among these subjects was compared with national incidence rates and with the incidence in an age- and sex-matched group of 2,779 non-IM students. No significant increase in cancer incidence was found. Three cases of Hodgkin's disease (HD) occurred in the IM group (1.3 cases expected), and one case occurred in the control group. All three post-IM cases of HD were in men. Intervals between diagnoses of IM and HD were 3, 4, and 7 yr. Only two other cases of lymphoma or leukemia were observed, and both were in the control group. (16 refs.)

77-7156 Nasopharyngeal Cancer among Young People in the United States: Racial Variations by Cell Type. (Eng) Greene, M. H. (Environmental Epidemiology Branch, NCI, NIH, Public Health Service, U.S. Dept. Health, Education, and Welfare, Bethesda, MD 20014); Fraumeni, J. F.; Hoover, R. *J Natl Cancer Inst* 58(5): 1267-1270; 1977.

US mortality and incidence statistics for nasopharyngeal cancer showed a fourfold excess risk of sarcomas (70% classified as rhabdomyosarcomas) in white children under age 10 and a four- to sevenfold excess of carcinomas in teenage blacks. Mortality from nasopharyngeal carcinoma (NPC) in young people was greater in the South than in the North, with the excess mortality in blacks linked to rural residence and low socioeconomic status. These and other characteristics of NPC in young persons suggest that environmental (perhaps infectious) agents are involved in this age group. These patterns contrast with NPC developing after age 25, when the rates predominated in Chinese Americans. Nasopharyngeal cancer in the US had three age peaks, with racial and epidemiologic distinctions that seemed to reflect different etiologies. (26 refs.)

77-7157 Age-Incidence and Risk of Diethylstilbestrol-related Clear Cell Adenocarcinoma of the Vagina and Cervix. (Eng) Herbst, A. L. (5841 S. Maryland Ave., Chicago, IL 60637); Cole, P.; Colton, T.; Robboy, S. J.; Scully, R. E. *Am J Obstet Gynecol* 128(1): 43-50; 1977.

Age-specific incidence rates and the cumulative risk of adenocarcinoma of the vagina and cervix after intrauterine exposure to diethylstilbestrol (DES) and similar compounds were calculated on the basis of 127 cases in women born after 1948. The results show a sharp rise in incidence beginning at age 14 and a peak at age 19. Women born in the period 1951-1953 had higher incidence rates than those born in the previous or subsequent 3-yr periods, which suggested that the pregnancy related use of DES peaked in the early 1950's. In DES-exposed women, the cumulative risk of genital clear cell

adenocarcinoma is 0.14 to 1.4/1,000 through age 24. The low risk of disease and the narrow age range of the cases, relative to the long latent period, suggest that DES is an incomplete carcinogen. Other factors, possibly related to puberty, may be involved in its carcinogenicity. (12 refs.)

77-7158 Rarity of Cancer of the Cervix in the Malaysian Orang Asli Despite the Presence of Known Risk Factors. (Eng) Sumithran, E. (Dept. Pathology, Medical Faculty, Univ. Malaya, Kuala Lumpur, Malaysia). *Cancer* 39(4): 1570-1572; 1977.

Cervical cancer is very rare in the Malaysian Orang Asli (Aborigines), despite the presence of factors associated with an increased risk of developing this malignancy. Of approximately 18,000 women admitted to the Gombak Orang Asli Hospital over a 13 yr period, only 3 had cervical tumors (squamous cell carcinomas). Malignant tumors of other sites were diagnosed in 78 women. In this aborigine community, the risk factors for cervical cancer include early age of first intercourse, multiparity, and noncircumcision of husbands. The low incidence of cervical cancer may be due to a strict moral code that limits extramarital sexual activity and associated venereal infection. (18 refs.)

77-7159 Etiologic Factors in the Pathogenesis of Liver Tumors Associated with Oral Contraceptives. (Eng) Nissen, E. E. (UCI Medical Center, Dept. Gynecology and Obstetrics, 101 City Drive S., Orange, CA 92668); Kent, D. R.; Nissen, S. E. *Am J Obstet Gynecol* 127(1): 61-66; 1977.

Data obtained from the recent literature (44 cases) and from the Registry for Liver Tumors Associated with Oral Contraceptives at the University of California (27 cases), pertinent to the use of oral contraceptive steroids and the appearance of hepatic focal nodular hyperplasia, adenoma, hamartoma, and hepatoma, were correlated. Eighty-five percent of the patients used the pill for > 4 continuous yr, indicating that prolonged usage is a significant etiologic factor. Seven combination oral contraceptives, three sequentials, and two progestogens alone were ingested by patients who developed liver tumors. Since 11 steroids (alone or in combination) are involved, it is possible that duration of use rather than specific chemical activity may be the more important etiologic factor. Mestranol and ethinyl estradiol (the only synthetic estrogens used in birth control pills) and progestogens have demonstrable effects upon coagulation, blood vessels, bile secretion, and liver enzymes. Decreased blood flow to the liver lobules produces hypoxia to the hepatocytes that, if severe, leads to cellular necrosis, with subcapsular or extracapsular rupture of the liver. This was seen in 18 patients, 8 of whom died. It is concluded that the continuous prolonged use of the pill should be avoided. (10 refs.)

77-7160 **Primary Liver Cell Carcinoma (PLCC) in the Northern Guinea Savanna of Nigeria.** (Eng) Fakunle, Y. M. (Dept. Medicine, Ahmadu Bello Univ., Zaria and Kaduna, Nigeria); Ajdukiewicz, A. B.; Greenwood, B. M.; Edington, G. M. *Trans R Soc Trop Med Hyg* 71(4): 335-337; 1977.

A total of 185 cases of primary liver cell carcinoma (PLCC) diagnosed at two hospitals in Nigeria during 1973 and 1974 were studied. The overall frequency of PLCC was 19.1% of all malignancies diagnosed, with a male to female ratio of 2:1. The peak incidence of PLCC occurred in men aged 20 to 49 yr. Results of hematologic tests showed that leukocytosis occurred in 16.7%. Major abnormalities of liver function included hypoalbuminemia (67% of cases) and hyperbilirubinemia (> 50%). Alkaline phosphatase activity was increased in 55/154 patients tested, α -fetoprotein was positive in 147/172 patients, and hepatitis B surface antigen (HBsAg) was found in 68/138 patients. The results confirm earlier observations of a strong association between HBsAg and PLCC. (20 refs.)

77-7161 **Epidemiology of Cancer of the Testis in Upstate New York.** (Eng) Graham, S. (State Univ. New York at Buffalo, Room 58, 4224 Ridge Lea Road, Amherst, NY 14226); Gibson, R.; West, D.; Swanson, M.; Burnett, W.; Dayal, H. *J Natl Cancer Inst* 58(5): 1255-1261; 1977.

Data on the 434 testicular cancer patients reported to the New York State Tumor Registry, 1960-1964, from upstate New York were compared with the data on 410 members of a random sample of the upstate population interviewed from 1959 to 1962. A high risk of developing seminomas and other types of testicular cancer was associated with professional occupations, native-born parentage, rural residence, and having been married, especially while young. These findings paralleled other studies of social characteristics associated with testicular cancer. Each of these factors carried a higher risk even when considered in the context of the other traits, and risk increased with increase in the number of characteristics possessed. (16 refs.)

77-7162 **Diet and Endocrine-related Cancer.** (Eng) Hill, P. (Lipid Metabolism, Naylor Dana Inst. Disease Prevention, Valhalla, NY 10595); Chan, P.; Cohen, L.; Wynder, E.; Kuno, K. *Cancer [Suppl]* 39(4): 1820-1826; 1977.

In female Sprague-Dawley rats given a single dose of 7,12-dimethylbenzanthracene (10 mg, po), a high-fat diet increased circulating prolactin levels during proestrus-estrus and increased the incidence of induced mammary tumors. Antiprolactin CB 154, which lowers the prolactin:estrogen ratio, reduced this tumor incidence and eliminated the differ-

ential effects of diet. In other studies, premenopausal Japanese women with breast cancer showed a significant decrease in plasma 17- β -estradiol levels compared with their Caucasian counterparts. The transfer of four healthy nurses to a vegetarian diet for 2 mo shortened their menstrual cycles by 1-2 days and decreased their prolactin and testosterone levels, indicating the important effect of diet on the menstrual cycle. Thus, high-fat diets enhance mammary tumor development in experimental animals and appear to cause hormonal changes and, subsequently, an altered breast cancer risk in women. (38 refs.)

77-7163 **Relation of Food Consumption to Cancer Mortality in Japan, with Special Reference to International Figures.** (Eng) Maruchi, N. (Sch. Health Sciences, Faculty Medicine, Univ. Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113, Japan); Aoki, S.; Tsuda, K.; Tanaka, Y.; Toyokawa, H. *Gann* 68(1): 1-13; 1977.

The relationship between food consumption and cancer mortality was examined in Japan and compared to that in Australia, Belgium, Canada, Denmark, England and Wales, Finland, France, Ireland, Israel, Italy, Sweden, Switzerland, Holland, New Zealand, Norway, South Africa, and the United States. Japan ranked near the top in per capita consumption of cereals, beans, fish, and vegetables - the traditional Japanese diet. Potatoes and starch, fruits, sugar, fats and oils, meat, eggs, and milk and dairy products constituted the westernized diet. Cancer of the esophagus, stomach, liver, and uterus was correlated with Japanese foods, whereas leukemia and cancer of the intestine, rectum, pancreas, lung, bladder, prostate, breast, and ovary were correlated with the westernized diet. Japan had the highest incidence of stomach and liver cancer among the 18 countries; it ranked low in the incidence of cancers associated with the westernized diet. However, Japan as a whole can be classified into three regions according to patterns of food consumption: traditional, urban (high milk and dairy product consumption), and Western. In the traditional areas, cancer of the intestine, lung, bladder, ovary, pancreas and uterus had a positive association with cereals, beans, fish, and vegetables; cancer of the esophagus, breast, and rectum had a positive association with fruits, sugar, fats and oils. In the urban areas, cancer of the intestine, lung, bladder, ovary, and uterus had a positive association with fruits, meat, eggs, and milk and dairy products. In the Western diet areas, leukemia and cancer of the prostate, liver, and uterus had a positive association with beans, fish, vegetables, potatoes and starch, and fruit. (18 refs.)

77-7164 **Diet and Metabolism: Large-bowel Cancer.** (Eng) Reddy, B. S. (Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY 10595); Mastromarino, A.; Wynder, E. *Cancer [Suppl]* 39(4): 1815-1819; 1977.

From a review of epidemiological studies, colon cancer appears to be linked with high dietary fat consumption and, perhaps, with a specific dietary component such as beef. Metabolic studies indicate that high fat intake affects fecal bile acids, neutral sterols, and bacteria. In high-risk Americans eating a mixed Western diet, large amounts of secondary bile acids, which act as colon tumor promoters in animal models, have been found in feces; in addition, fecal bacteria contained higher β -glucuronidase activity. Patients with familial polyposis showed an increase in the fecal excretion of cholesterol and a decrease in its microbial metabolite, coprostanol, indicating decreased bacterial degradation of cholesterol. In addition, the activity of fecal 7 α -dehydroxylase, which converts cholic acid and chenodeoxycholic acid to the two secondary bile acids deoxycholic acid and lithocholic acid, respectively, was higher in patients with colon cancer than in controls. Both fecal bacterial enzymes and fecal steroids appear to be implicated in colon cancer. (33 refs.)

77-7165 Statistical Data on Gastric Cancer Morbidity in the Estonian SSR During 1963-1972. (Rus)

Rakhu, M. A. (Inst. Experimental and Clinical Medicine, Ministry Health Estonian SSR, USSR). *Vopr Onkol* 23(5): 41-45; 1977.

Epidemiological data on gastric cancer morbidity in 100,000 inhabitants of the Estonian SSR, USSR, are presented for the years 1963-1972. The crude morbidity rates for men are 65.2/100,000 for 1963-1967 and 68.1 for 1968-1972; those for women are 57.8 and 46.4, respectively. The age adjusted morbidity rates for men are 63.5 for 1963-1967 and 58.2 for 1968-1972 (urban dwellers), and 57.7 for 1963-1967 and 49.5 for 1968-1972 (rural dwellers). The age-adjusted morbidity rates for men aged 35-64 yr are 98.2 (1963-1967) and 87.1 (1968-1972). The age-adjusted morbidity rates for women are 35.4 for 1963-1967 and 28.3 for 1968-1972 (urban dwellers), and 31.9 for 1963-1967 and 24.4 for 1968-1972 (rural dwellers). The morbidity rates for women aged 35-64 yr are 49.4 for 1963-1967 and 40.4 for 1968-1972. The diagnosis was verified microscopically in 38.3%-61.3% of men and 27.1%-47.7% of women. The cancer patients included Russians that had immigrated to Estonia from areas with high gastric cancer morbidity. The statistical data indicate that the morbidity increased among urban dwellers during 1968-1972 compared with 1963-1967, the age-adjusted morbidity decreased during the second period, and the male-to-female ratio increased from 1.8 for 1963-1967 to 2.0-2.1 for 1968-1972. (19 refs.)

77-7166 Incidence and Diagnosis of Gastric Cancer in Outpatient Clinics. (Rus) Zhivetskii, A. V.

(Dept. Oncology, Chernovtsy Medical Inst., Chernovtsy, USSR); Andrusenko, V. A.; Bodnar, G. V.; Balan, I. V. *Klin Khir* (5): 10-13; 1977.

Epidemiological and diagnostic aspects of gastric cancer in Moldavia, USSR, are described. Gastric cancer is the most frequent neoplastic disease in Moldavia; the morbidity is 30.1/100,000 inhabitants (60.4% men, 39.6% women). The morbidity is highest in persons > 50 yr of age, especially those aged 60-69 yr (40.4% of all male patients, 34.5% of all female patients). The case histories of 250 gastric cancer patients revealed precancerous conditions in 52.6% (hypochlorhydric gastritis in 24%, hyperchlorhydric gastritis in 17.1%, peptic ulcer in 10.2%, and polyposis in 1.3%), deviations from normal dietary habits in 85% (predominance of cold solid food and insufficient mastication), overeating in 49%, preference for excessively hot food in 78%, alcohol abuse in 92%, and smoking in 96%. The respective percentages of blood groups O, A, B, and AB were 21.2%, 37.8%, 22.6%, and 18.4%. Adenocarcinoma was diagnosed in 64.4%, scirrhous carcinoma in 15.2%, poorly differentiated carcinoma in 12.3%, solid carcinoma in 4.1%, mucous carcinoma in 2.7%, and colloid carcinoma in 1.3%. The histories of 644 other patients revealed hypochromic anemia at early stages of the disease in 8.8%, anisocytosis and poikilocytosis in 7.8%, and dysproteinemia due to a reduced serum albumin level and an increased globulin level in 84.5%. (15 refs.)

77-7167 Decline of Stomach Cancer Mortality Rates in a High Risk Geographical Area. (Eng) Zaldivar, R.

(International Res. Group for Cancer Epidemiology and Human Ecology, Miami, FL). *Osterr Z Onkol* 3(5/6): 115-116; 1977.

Gastric cancer death rates per 100,000 population were examined by sex and age groups in Chile for a 34-yr period (1941-1974). The yearly change in gastric cancer mortality rates, calculated by linear regression analysis for both males and females in 10-yr cohorts from 25 to 74 yr of age, and age-adjusted death rates for persons aged 25-74 yr showed negative regression coefficients, all being statistically highly significant. This marked decline in stomach cancer mortality was associated with an increase in consumption of milk, animal proteins (meat and fish), sugar, and fish, as well as fats, oils, and butter. Recent epidemiological studies have shown a correlation between nitrate fertilizers and gastric cancer mortality in Chile. It is suggested that data on the total nitrate nitrogen levels in the diet of people living in high- and low-risk areas for stomach cancer could be valuable in the search for etiological variables. (12 refs.)

77-7168 Statistics Point to High-Cancer Localities. (Eng) Mason, T. (NIH, Bethesda, MD 20014).

Occup Health Saf 46(3): 44-48; 1977.

An analysis of US cancer mortality (1950-1969) at the county

or state economic level revealed excessive mortality from (1) oral cancer in the industrial northeast and in scattered urban areas across the country, (2) bladder cancer in white men and women in 21 New Jersey counties, and (3) lung cancer in men along the Gulf Coast from Texas to Florida. The geographic distribution of the oral and bladder cancers is suggestive of occupational exposure to textile and chemicals, respectively. The distribution of lung cancer is suggestive of exposure to asbestos in the shipbuilding industry or of risks associated with the pulp- and paper-processing industries. (no refs.)

- 77-7169 **The Changing Histopathology of Lung Cancer. A Review of 1682 Cases.** (Eng) Vincent, R.G. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY 14263); Pickren, J. W.; Lane, W. W.; Bross, I.; Takita, H.; Houten, L.; Gutierrez, A. C.; Rzepka, T. *Cancer* 39(4): 1647-1655; 1977.

A review of histopathologic findings in 1,682 lung cancer patients treated from 1962 to 1975 indicated that adenocarcinoma is now the most prevalent form of lung cancer. It increased progressively from 17.0% of the total cases in 1962 to 29.8% by 1975. Factors that may contribute to this increased prevalence include (1) changes in the criteria for reading histologic slides; (2) the increased incidence of lung cancer in women, who have a propensity for adenocarcinoma; and (3) occupational and environmental factors. The data suggest that lung cancer death rates may increase, since the 18-mo survival for adenocarcinoma is substantially lower than that for squamous cell carcinoma, which had been the most prevalent form of the disease. If the smoking habits of women continue to approximate those of men, lung cancer incidence and mortality should be similar in both sexes. (32 refs.)

- 77-7170 **Lung Cancer among Black Migrants. Interaction of Host and Occupational Environment Factors.** (Eng.) Mancuso, T. F. (Dept. Industrial Environmental Health Sciences, Univ. Pittsburgh, Pittsburgh, PA 15261). *J Occup Med* 19(8): 531-532; 1977.

The hypothesis that biological and social imprints (poverty, malnutrition, genetics), endemic factors in the early years of life, combine with subsequent migration and environmental stresses to bring about biological imbalances that increase susceptibility to disease, disability, and mortality risks was explored. In an Ohio study, an increased lung cancer risk (100% excess) was found among black migrants born in the South compared with blacks born in Ohio. Similarly, white migrants from the South showed a 50% increased risk for lung cancer compared with white native-born Ohio residents. Migrants had a substantially higher rate of mortality from pneumoconiosis than native-born residents. A prospective study of death and relative risk of dying from lung cancer

in 2,543 coke plant workers identified migration as a contributing factor. Examination of the death certificates revealed that 33/35 deaths of black men occurred among those born in the South. (4 refs.)

- 77-7171 **Arsenic Absorption in Steel Bronze Workers.** (Eng) Clay, J. E. (Employment Medical Advisory Service, Birmingham, England); Dale, I.; Cross, J. D. *J Soc Occup Med* 27(3): 102-104; 1977.

Occupational investigations for the presence of arsenic were performed following arsine poisoning in a steel bronze worker. The threshold limit value of arsenic (0.5 mg/meters³) had not been exceeded in the atmosphere; but markedly raised arsenic content was detected by neutron activation in the pubic hair and toe nails of the workers, indicating that the arsenic had been ingested. Arsenic was found on a number of the work surfaces around the factory. The carcinogenic hazard of industrial arsenic is discussed. (10 refs.)

- 77-7172 **The Effect of Industrial Environment on the Incidence of Skin Neoplasms in the Population of Lodz During 1965-1974.** (Pol) Czernielewska, I. (Dzial Higieny Pracy Wojew. Stacja Sanitarno-Epidem., ul. Wodna, 90-046 Lodz, Poland); Chrominska, H. *Nowotwory* 27(2): 159-168; 1977.

From 1965 to 1974, 1,092 cases of skin neoplasm were diagnosed in 471 male and 621 female residents of Lodz. The incidence was 14.4/100,000 inhabitants: 13.4/100,000 for men and 15.2/100,000 for women. The incidence increased markedly with age from 0.8/100,000 in men and 0.7/100,000 in women < 39 yr old to 109.6/100,000 in men and 125.9/100,000 in women > 80 yr old. Most patients were > 60 yr old, and the mean age at onset was 63.2 yr in men, 66.2 yr in women. The standardized incidence was 18.4/100,000 in men, 21% higher than that in women. Basal cell carcinoma was diagnosed in 356 men and 499 women, squamous cell carcinoma in 111 men and 104 women, other skin cancers in 4 men and 18 women. Squamous cell carcinoma was localized mainly to the auricles, trunk, and extremities, and, especially in women, to the nose. An inquiry revealed occupational exposure to carcinogenic agents in 178 patients: oils and lubricants in 149, soot in 14, tar and asphalt in 4, and UV radiation in 11. (19 refs.)

- 77-7173 **Asbestos Risk Studies.** (Eng) Anonymous (No affiliation given). *Am Ind Hyg Assoc J* 38(5): A-6; 1977.

In an attempt to detect cancer, a group of former asbestos workers in a Texas community have been hospitalized every 6 mo for a complete physical examination. Those workers who smoked are judged to be at a 92 times greater risk than non-smokers who have not been exposed to asbestos. Effects of asbestos exposure seem to appear after a 20-30 yr dormant period. (no refs.)

77-7174 Cell Proliferation Kinetics in Enterocytes from Experimental Colonic Tumors of Rats. (Rus)

Pozharisskii, K. M. (Lab. Experimental Tumors, Scientific Res. Inst. Oncology, Leningrad, USSR); Klimashevskii, V. F.; Gushchin, V. A. *Tsitologiya* 19(5): 537-549; 1977.

The proliferation kinetics of enterocytes from the normal colon and colonic adenocarcinomas induced by 1,2-dimethylhydrazine hydrochloride (21 mg/kg/wk sc for 5-6 mo) was studied histoautoradiographically in mongrel male rats. The labeled mitosis curves obtained for the adenocarcinoma and the normal colon were similar, but the duration of the short mitotic cycle was 16 hr in the former vs 11 hr in the latter. The increase was mainly due to a prolongation of the G₁ phase and to a more pronounced heterogeneity of the mean durations of S and G₂, as well as to the appearance of the subpopulation R₂. The labeled saturation curve for the adenocarcinoma was similar to that for the basal part of the crypts, where there are various cell subpopulations, possibly also stem enterocytes. This similarity indicates that the adenocarcinoma also consists of subpopulations with different proliferation rates and that the proliferation parameters of the adenocarcinoma cells are similar to those of the stem enterocytes of normal intestinal epithelium. The findings indicate intense proliferation of the adenocarcinoma cells, even though the rate is lower than that of normal enterocytes in the zone of max proliferation. (28 refs.)

77-7175 Effect of Different Sex of Tumour Bearing Mice and of Ovariectomy on the Proliferation Kinetics of a Solid Transplantable Mammary Carcinoma (C3H-Mouse). (Eng) Feaux de Lacroix, W. (Inst. Pathology, Univ. Koln, Josef-Stelzmann-Str. 9, D-5000 Koln 41, W. Germany); Hensen, F. J.; Klein, P. J.; Nola, E.; Lennartz, K. J. *Z Krebsforsch* 87(2): 181-191; 1976.

The growth of a solid, transplantable mammary carcinoma was continuously measured in female, ovariectomized female, sham-operated female and male C3H mice. The cell cycle, growth fraction, and cell loss factor were determined by autoradiography. According to the growth curves, the increase in the tumor volume as a function of time was delayed in ovariectomized or male mice compared to normal females. The tumor attained different max mean volumes in the four experimental groups, the largest being in intact and sham-operated females and the smallest in ovariectomized females and males. The delay in tumor growth was due to the longer cell cycle time of tumor cells in ovariectomized and male animals, attributed mainly to a prolonged presynthetic gap. Significant differences in growth fraction and cell loss factor were not seen among the four groups. These results indicate that the solid transplantable mammary carcinoma is only weakly responsive to sex hormones, a conclusion that correlates well with the low number of specific estrogen receptors detected in the tumor cells. (27 refs.)

See also:

*(Rev.): 77-6612, 77-6621, 77-6622, 77-6624, 77-6625, 77-6627, 77-6628, 77-6630, 77-6633, 77-6640, 77-6664, 77-6665.

*(Chem.): 77-6737, 77-6738, 77-6768, 77-6796, 77-6803, 77-6818, 77-6825, 77-6827, 77-6852.

*(Phys.): 77-6882, 77-6885, 77-6887, 77-6888, 77-6891, 77-6898, 77-6910, 77-6914.

*(Viral): 77-6989, 77-6998.

*(Path.): 77-7105, 77-7113.

MISCELLANEOUS

7-7176 **Standardization of the Chromium-51 Release, Cell-mediated Cytotoxicity Assay: Cryopreservation of Mouse Effector and Target Cells.** (Eng) Holden, C. T. (Lab. Immunodiagnosis, NCI, NIH, Public Health Service, US Dept. Health, Education, and Welfare, Bethesda, MD 20014); Oldham, R. K.; Ortaldo, J. R.; Herberman, R. B. *J Natl Cancer Inst* 58(3): 611-622; 1977.

Controlled cryopreservation techniques were used to standardize the ^{51}Cr -release cytotoxicity assay, thus ensuring reliable comparisons between results obtained on different days in a murine sarcoma virus (MSV) tumor system. Optimal conditions for freezing of both effector and target cells were similar. Dimethyl sulfoxide (DMSO: 7.5%-10.0%) was the cryoprotective agent, and cells were frozen at the rate of 1 min. Factors affecting recovery of functional reactivity were related to the toxicity of DMSO for the cells, the osmotic stress placed on the cells when the DMSO was removed after thawing, the handling temperature of the freshly thawed cells, and the susceptibility of cells to mechanical damage immediately after thawing. The recovery of lymphocytes after freezing was about 70%; the recovery of cytotoxicity was about 85%. Syngeneic cytotoxic reactivity induced by cocultivation with Moloney MSV was cryopreserved, as were allogeneic cytotoxicity and natural cytotoxic reactivity. Multiple tests employing effector cells from the same frozen pool gave reproducible results. Cryopreserved target cells gave decreased day-to-day variability in susceptibility to lysis, since the same population of cells could be employed in each assay. These results demonstrate that a constant source of effector cells and target cells can be made available for in vitro assays of cell-mediated immunity. (36 refs.)

7-7177 **Interacting Cell Populations in Cultures of Leukocytes from Normal or Leukemic Peripheral Blood.** (Eng) McCulloch, E. A. (Ontario Cancer Inst., 70 Sherbourne St., Toronto, Ontario M4X 1K9, Canada); McCulloch, E. A.; J. E. *Blood* 49(2): 269-280; 1977.

Genetic studies in cultures containing 2×10^5 peripheral WBC from acute myeloblastic leukemia patients revealed extensive, radiation-sensitive increases in thymidine (TdR) incorporation without parallel increases in cell number. WBC conditioned medium prepared with phytohemagglutinin (PHA) or PHA alone induced a modest and variable stimulation of ^3H -TdR incorporation. Stimulation was always observed with the method of limiting dilution, and it ranged from 3- to 29-fold in individual patients. Mixing small numbers of intact cells with larger numbers of irradiated cells provided quantitative evidence of cellular interactions between irradiated, PHA-stimulated populations and a sub-

population capable of ^3H -TdR incorporation. Similar evidence for cell-cell interaction was obtained for normal WBC. (22 refs.)

77-7178 **Identification and Kinetics of G_1 Phase-confined Cells in Experimental Mammary Carcinomas.** (Eng) Potmesil, M. (Cancer and Radiobiological Res. Lab., Dept. Biology, New York Univ., New York, NY 10003); Goldfeder, A. *Cancer Res* 37(3): 857-864; 1977.

The various types of nucleoli in parenchymal cells from dbrB, DBAH, and MT2 mammary tumors growing in DBA/1J, DBA/2J, and X/Gf mice, respectively, were investigated. The number of cells with trabeculate (TN) or ring-shaped nucleoli (RSN) or nucleolar fragments (NF) was closely related to the growth rate and degree of differentiation of the tumors. All three subpopulations increased with increasing age and with decelerated tumor growth. In some cells in late telophase, TN or RSN could be distinguished at the poles, indicating that the cells were halted in G_1 . Cells with these nucleoli had a DNA content close to $2c$; cells with dense nucleoli had a DNA content corresponding to either $2c$, $2c-4c$, $4c$, or $> 4c$. These findings indicate that cells with TN and RSN and cells with NF either proceed slowly through G_1 or are halted in this phase. Cells with TN were replaced steadily, having a transit time of ≤ 84 hr. They constituted a fast component of cell renewal of G_1 -confined cells. A slow component, cells bearing RSN or NF, were replaced after a lag of 24 to 48 hr; the residency time for some of these cells was > 84 hr. Thus, cells with dense nucleoli represent the proliferating pool and cells with TN, RSN, and NF represent the nonproliferating pool. (22 refs.)

77-7179 **Transient Inhibition of Initiation of S-Phase Associated with Dimethyl Sulfoxide Induction of Murine Erythroleukemia Cells to Erythroid Differentiation.** (Eng) Terada, M. (Dept. Human Genetics and Development, Columbia Univ., New York, NY 10032); Fried, J.; Nudel, U.; Rifkind, R. A.; Marks, P. A. *Proc Natl Acad Sci USA* 74(1): 248-252; 1977.

The cell cycle of the murine erythroleukemia cell (MELC) line in suspension culture was analyzed during differentiation induced by dimethyl sulfoxide Me_2SO . Thymidine incorporation, the thymidine labeling index, and the relative DNA content per cell (as measured by flow microfluorometry) demonstrated a transient inhibition of cell entry into the S phase, which was detected as early as 5 hr and was max at 20 hr

after beginning of nonsynchronous cultures. In the presence of the Me_2SO , there was restricted binding of the intercalating dye propidium iodide to the chromatin of cells in G_1 as early as 10 hr of culture. This restricted binding was also observed in MELC cultured with other inducing agents, such as butyric acid and dimethylacetamide, but not with an Me_2SO -resistant cell line cultured with Me_2SO . It is suggested that induction to erythroid differentiation involves a series of events that includes (1) a triggering event related to the prolongation of G_1 , which is associated with restricted binding of intercalating dyes to chromatin, (2) the subsequent S phase of the cell cycle, and (3) additional stabilizing events that occur after the S phase that are required to render differentiation irreversible. (36 refs.)

- 77-7180 Aprotinin and Growth of Walker 256 Carcinoma in the Rat.** (Eng) Thomson, A. W. (Dept. Pathology, Univ. Medical Buildings, Foresterhill, Aberdeen, Scotland); Pugh-Humphreys, R. G.; Horne, C. H.; Tweedie, D. J. *Br J Cancer* 35(4): 454-460; 1977.

The effect of aprotinin on the growth of Walker 256 carcinoma in male Sprague-Dawley rats was investigated after injection of 5×10^6 tumor cells im or 10^6 tumor cells ip or iv. Twice-daily injections of 2 ml aprotinin ip starting on day 3 after tumor cell injection resulted in fewer deaths on days 6-11. In other studies, administration of aprotinin twice daily from day 0 or day 3 did not result in any significant difference in tumor size compared to saline-treated controls by 8 days. Furthermore, the degrees of tumor necrosis and WBC infiltration were comparable between the treated and control groups. There was no decrease in invasiveness in the treated group. Pulmonary tumor colony formation was examined in rats given saline, aprotinin from day 0, or aprotinin from day 3. The incidence of colonies decreased when aprotinin was first given on day 0, but when it was first given on day 3, 25% of the rats had more colonies than controls. These findings indicate that aprotinin is not an effective antitumor agent. (34 refs.)

- 77-7181 Properties of a Baby-Hamster-Kidney Cell Line with Increased Resistance to 2-Deoxy-D-glucose.** (Eng) Meager, A. (Natl. Inst. Medical Res., Ridge-way, Mill Hill, London NW7 1AA, England); Nairn, R.; Hughes, R. C. *Eur J Biochem* 72(2): 275-281; 1977.

The effects of 2-deoxy-D-glucose on various properties of baby hamster kidney 21/C13 cells, especially those relating to glycosylation reactions, were investigated to determine whether cellular glycoproteins are a factor in 2-deoxy-D-glucose toxicity. The study indicated that toxicity was not mediated through the effects of cell glycoproteins on glycosylation. (30 refs.)

- 77-7182 Rates of Aggregation, Loss of Anchorage Dependence, and Tumorigenicity of Cultured Cells.** (Eng) Wright, T. C. (Dept. Pathology, Harvard Medical Sch., 25 Shattuck St., Boston, MA 02115); Ukena, T. E.; Campbell, R.; Karnovsky, M. J. *Proc Natl Acad Sci USA* 74(1): 258-262; 1977.

The initial net rate of spontaneous aggregation of cells suspended with EDTA was measured for various cell types, including spontaneous transformants and cells transformed by DNA and RNA viruses and correlated with loss of anchorage-dependence determined by growth in methylcellulose and tumorigenicity in vivo. All cells that had lost their anchorage-dependence and were tumorigenic showed a high net rate of spontaneous adhesion. Of the 16 cell types examined, only 1 nontumorigenic cell line (the A31 clone of Balb 3T3 cells) had a net aggregation rate that fell within the range of the tumorigenic group. Experiments with concanavalin A (Con A) indicated that Con A-induced agglutination and spontaneous aggregation do not proceed by the same mechanism, because not all cells that showed high rates of spontaneous aggregation were agglutinated by Con A. In addition, the net spontaneous aggregation rate appears to be more closely correlated with tumorigenicity than the Con A-induced agglutination rate. It is concluded that the spontaneous aggregation assay is a quick and reliable index of tumorigenicity. (32 refs.)

- 77-7183 Altered Morphology and Increased Adhesiveness of Chinese Hamster Ovary Cells Cultured on Fibrin.** (Eng) Nozawa, R. T. (Dept. Bacteriology, Juntendo Univ. Sch. Medicine, Hongo, Tokyo 113, Japan). *J Cell Physiol* 90(2): 351-359; 1977.

The effects of cultivating Chinese hamster ovary cells (CHO) on fibrin on cell behavior, including adherence, growth, and fibrinolysis, were examined in order to simulate tumor cell behavior in vivo. In contrast to the epithelioid morphology of sparsely plated cells on plastic dishes, cells on fibrin assumed a round shape and then converted to a stretched form with protruded processes that increased with cell density. Within a few days, cells fibrinolysed the adjacent fibrin and returned to the morphology seen in plastic dishes. When fibrinolysis was inhibited by ϵ -aminocaproic acid (BACA), cells continued to grow on the fibrin for a longer period and showed dense, criss-crossed, fibroblast-type congestion. Cells on plastic, however, maintained a pavementlike epithelioid appearance when they grew to a confluent monolayer. Another altered characteristic of CHO cells on fibrin, maintained by the addition of EACA, was an increased accumulation of cells in multilayers. A possible explanation for this increased cell accumulation is that the altered surface properties of the stretched cells on fibrin makes them more adhesive, so that newly divided cells stick on the preformed cell layers. A possible link of the characteristics of cells on fibrin to tumor cell behavior in vivo is discussed. (18 refs.)

77-7184 **Regulation of Mammalian Protein Synthesis In Vivo. Stimulated Protein Synthesis in Liver In Vivo after Cycloheximide Treatment.** (Eng) Ch'ih, J. J. (Dept. Biological Chemistry, Hahnemann Medical Coll. and Hosp., Philadelphia, PA 19102); Procyk, R.; Devlin, T. M. *Biochem J* 162(3): 501-507; 1977.

Changes in the synthesis of extra- and intracellular proteins were studied in the male Wistar rat liver following ip injection of 2.0 mg/kg cycloheximide. Following a brief period of protein synthesis inhibition, the liver rapidly adapted to the altered state. Fibrinogen was synthesized early in the adaptive phase, suggesting that an extracellular protein was first synthesized to help maintain homeostasis. (21 refs.)

77-7185 **Association of Decreased Membrane Protein Phosphorylation with Red Blood Cell Spherocytosis.** (Eng) Matsumoto, N. (Dept. Medicine, Univ. Minnesota Medical Sch., Minneapolis, MN 55455); Yawata, Y.; Jacob, H. S. *Blood* 49(2): 233-239; 1977.

A close association between sphering of human RBC and deficient phosphorylation of their membrane proteins by endogenous ATP was demonstrated in the genetic error of hereditary spherocytosis and in cells rendered spheroidal by exposure to elevated temperatures or to the sulfhydryl inhibitors N-ethylmaleimide and paramercuribenzoate. At temperatures > 48 C or at N-ethylmaleimide concentrations > 2 moles/ml RBC, the onset of sphering coincided with the development of deficient ghost protein phosphorylation. The possibility that protein kinase is involved in RBC shape regulation is discussed. (30 refs.)

77-7186 **A New Amino Acid Derivative Present in Crown Gall Tumor Tissue.** (Eng) Kemp, J. D. (Plant Disease Resistance Res. Unit, ARS, USDA, Dept. Plant Pathology, Univ. Wisconsin, Madison, WI 53706). *Biochem Biophys Res Commun* 74(3): 862-868; 1977.

The presence of amino acid derivatives was examined in primary and secondary sunflower crown gall tissue cultures and in fresh crown gall tumors from sunflower plants inoculated with *Agrobacterium tumefaciens* B₆. A previously undetected amino acid derivative was found in both the tissue cultures and the fresh tumor samples, but not in normal sunflower tissue. Radioactive labeling and cochromatography indicate that the natural derivative is identical to synthetic N²-(carboxyethyl)-L-histidine (histopine). Crown gall tissue cultures contained 1 micromole histopine/20 g fresh wt. Histopine was utilized by *A. tumefaciens* strain B₆ but not by strain C₅₈. Histopine therefore appears to be strain-specific, similar to the other known amino acid derivatives. (12 refs.)

77-7187 **Carbonic Anhydrase Isozymes in Cultured Friend Leukemic Cells.** (Eng) Stern, R. H. (Rosenstiel Center, Brandeis Univ., Waltham, MA 02154); Boyer, S. H.; Conscience, J. F.; Friend, C.; Margolet, L.; Tashian, R. E.; Ruddle, F. H. *Proc Soc Exp Biol Med* 156(1): 52-55; 1977.

Carbonic anhydrase isozymes I and II (CA I and CA II) were assayed in cultured Friend leukemic cells by radial immunodiffusion. In dimethyl sulfoxide-treated cultures, CA I levels remained constant or decreased, but CA II levels increased. However, in untreated control cultures both CA I and CA II levels increased. (11 refs.)

77-7188 **Partial Purification and Characterization of a Translational Inhibitor from Friend Leukemia Cells.** (Eng) Pinphanichakarn, P. (Clayton Foundation Biochemical Inst., Dept. Chemistry, Univ. Texas, Austin, TX 78712); Kramer, G.; Hardesty, B. *J Biol Chem* 252(6): 2106-2112; 1977.

The purification and characterization of a translational inhibitor present in the Friend leukemia cell (FLC) line F4H-2, a variant of FSD 1/clone 4, are described. The inhibitor (FLC inhibitor B) has an estimated mol wt of 214,000 and a max absorbance at 280 nanometers; it is heat-labile and sulfhydryl reagent-insensitive. It inhibits protein synthesis at a step of peptide chain initiation by preventing initiation factor-dependent binding of methionyl-transfer (t)RNA-f to 40S ribosomal subunits. However, it does not interfere with the formation of the ribosome-independent ternary complex among initiation factor IF-E₂, methionine-tRNA-f, and guanosine triphosphate. The inhibitor preparation contains protein kinase activity, which phosphorylates the smallest subunit of IF-E₂. A comparison of the functions of FLC inhibitor B with the hemin-controlled repressor of reticulocytes indicated a functional similarity between the two. (50 refs.)

77-7189 **DNA Synthesis in Permeable Mouse Ascites Sarcoma Cells.** (Eng) Seki, S. (Dept. Biochemistry, Cancer Inst., Okayama Univ. Medical Sch., 2-5-1, Shikata-cho, Okayama 700, Japan); Oda, T. *Cancer Res* 37(1): 137-144; 1977.

A permeable cell system was used to study DNA synthesis in an ascites sarcoma induced in a C3H/He mouse by the Schmidt-Ruppin strain of Rous sarcoma virus. The ascites cells were made permeable to nucleoside triphosphates by treatment with a hypertonic buffer. DNA synthesis in the permeable cells was stimulated approx 50% by the addition of 0.05-0.5 milliM cytidine triphosphate, guanosine triphosphate and uridine triphosphate to assay mixtures containing ATP and four deoxyribonucleoside triphosphates. DNA replication was confined to the nucleus and was sensitive to

N-ethylmaleimide and DNase. The activity assayed by the permeable cell system correlated with the DNA replicating activity assayed by ^3H -deoxythymidine incorporation in intact cells. This correlation between in vitro and in vivo DNA synthesis was confirmed in synchronized ascites sarcoma cells. Approx 60% of the DNA synthesized in permeable cells was due to elongation of the strands initiated in vivo. (21 refs.)

- 77-7190 **Nuclear DNA Polymerases of Human Carcinomas.** (Eng) DePhilip, R. M. (Dept. Anatomy and Cell Biology, Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA 15261); Lynch, W. E.; Lieberman, I. *Cancer Res* 37(3): 702-704; 1977.

The DNA polymerases of normal human lung and cecum, primary carcinomas of the human lung, breast, and cecum, and resting and regenerating rat liver were compared. Sucrose gradient analysis revealed similarities between the enzymes of normal human tissue and unstimulated rat liver and between those of human carcinoma and regenerating rat liver. The human tissues contained two polymerases with sedimentation coefficients of 3S and 7S; these enzymes were restricted to the nucleus, and the specific activity of the 7S polymerase was elevated in the carcinomas. As with the regenerating rat liver polymerases, the 3S activity of a bronchogenic carcinoma was unaffected by cytosine arabinoside 5'-triphosphate and reduced only a little by novobiocin. In contrast, the activity of the 7S enzyme was abolished by both compounds. A variety of other inhibitory agents had similar effects on the 7S polymerases of the human carcinomas and regenerating rat liver. The possibility that this enzyme is involved in nuclear DNA replication is discussed. (8 refs.)

- 77-7191 **Effect of Concanavalin A on Tyrosine Amino-transferase in Rat Hepatoma Tissue Culture Cells. Rapid Reversible Inactivation of Soluble Enzyme.** (Eng) Gopalakrishnan, T. V. (Molecular Hematology Branch, Natl. Heart and Lung Inst., NIH, Bethesda, MD 20014); Thompson, E. B. *J Biol Chem* 252(8): 2717-2725; 1977.

The effect of different concentrations of concanavalin A (Con A) on tyrosine aminotransferase (TAT) activity in FU-5-5 and HTC-H1 rat hepatoma cells in vitro was investigated. In growth medium containing $> 25 \mu\text{g/ml}$ Con A, the level of the enzyme decreased with increasing concentrations of Con A, with a max effect occurring at $200 \mu\text{g/ml}$; no further effect was seen with concentrations up to $500 \mu\text{g/ml}$. However, when Con A was added after the growth medium was replaced with fresh saline containing Ca^{+2} and Mg^{+2} , the max effect of Con A was seen at a concentration of $50 \mu\text{g/ml}$. In the remaining experiments, a concentration of $200 \mu\text{g/ml}$ was used to ensure max inactivation. The process was found to be temperature-dependent and independent of de novo pro-

tein and RNA synthesis. The inactivation could be reversed by adding 0.1 ml of 0.5 M α -methyl-D-mannopyranoside, a competing sugar for Con A binding. Other lectins known to bind different sugars did not bring about inactivation. Con A did not bring about the inactivation of lactic dehydrogenase, another soluble enzyme. Maintenance of the inactive form of TAT after the binding of Con A to the cells required the continued presence of the lectin. Incubation of cell extracts with Con A did not result in inactivation, nor did mixing of extracts from treated cells with extracts from untreated cells. Further studies indicated that transcription of messenger RNA for the enzyme continued, even though the finished product was inactive. However, the max induction level after addition of α -methyl-D-mannopyranoside was about half normal, possibly due to impairment of protein synthesis by Con A. These findings indicate that there are two requirements for the inactivation of TAT by Con A: the binding of native Con A to the cells and integrity of certain structural elements of the cells. (35 refs.)

- 77-7192 **Adenosine Triphosphatases as Histochemical Markers for the Cell of Origin in Experimental Mammary Carcinoma.** (Eng) Russo, J. (Experimental Pathology Lab., Dept. Biology, Michigan Cancer Foundation, Detroit, MI 48201); Wells, P. A.; Russo, I. H. *Cancer Res* 37(4): 1088-1098; 1977.

Different ATPase activities were studied at the ultrastructural level in order to differentiate epithelial and myoepithelial cells in normal and neoplastic mouse mammary tissues. Mg^{2+} -dependent and $\text{Na}^{+}\text{-K}^{+}$ -dependent ATPase activities were studied in the BALB/c mouse mammary gland; a BALB/c carcinoma from a transplantable D2 hyperplastic nodule; a stable cell line, MCF-8, derived from the BALB/c carcinoma; and a BALB/c scirrhouslike carcinoma induced by MCF-8 cell injection. Mg^{2+} -dependent ATPase was detected in the plasma membranes of normal mouse mammary epithelial cells, the epithelial component of the BALB/c carcinoma, the MCF-8 cells in culture, and the atypical epithelial component of the scirrhouslike carcinoma. $\text{Na}^{+}\text{-K}^{+}$ -dependent ATPase was not present in the plasma membranes of any mammary epithelial cells. Both $\text{Na}^{+}\text{-K}^{+}$ -dependent and Mg^{2+} -dependent ATPase were localized in the plasma membranes of the myoepithelial cells of the normal mammary gland and the BALB/c carcinoma. These results show that both the BALB/c carcinoma and the scirrhouslike carcinoma originated in mammary epithelial cells rather than in myoepithelial cells. These results also indicate that the MCF-8 cell line was derived from the epithelial component of the primary BALB/c carcinoma. These conclusions were supported by the presence of intracisternal A-type viral particles in the epithelial cells of the primary BALB/c carcinoma, the MCF-8 cells in culture, and the epithelial cells of the scirrhouslike carcinoma. Thus, the enzymatic markers were specific for cell type and remained unchanged by cell transformation. (22 refs.)

- 77-7193 Cell-Cycle-related Changes of 3':5'-Cyclic GMP Levels in Novikoff Hepatoma Cells. (Eng.) Zeilig, C. E. (Dept. Pharmacology, 4200 E. Ninth Ave., C-236, Univ. Colorado Medical Center, Denver, CO 80262) Goldberg, N. D. *Proc Natl Acad Sci USA* 74(3): 1052-1056; 1977.

Intracellular and extracellular levels of 3':5'-cyclic guanosine monophosphate (cGMP) and 3':5'-cAMP were studied in synchronized Novikoff rat hepatoma cells. Intracellular levels of cGMP increased spontaneously from 2 (without colcemid) to 10 (with colcemid) times, in proportion to the number of cells in mitosis. As cells entered mitosis, cellular cAMP decreased simultaneously with the rise in GMP. These reciprocal changes in cyclic nucleotide levels were reversed as cells passed out of metaphase and through anaphase. Max cAMP and minimum cGMP concentrations occurred during G₁. Less marked reciprocal fluctuations were also seen in the S phase and early G₂, where the ratio of cAMP to cGMP concentrations first fell and then increased. These changes in cyclic nucleotide ratios were closely correlated with major cell-cycle transitions at the boundaries between G₁/S, S/G₂, G₂/prophase, and metaphase/anaphase. Colcemid or vinblastine completely prevented the appearance of extracellular cAMP, but augmented the appearance of extracellular cGMP in parallel with the accumulation of mitotic cells. These results indicate that increased intracellular turnover of cGMP and cAMP occurred before and after metaphase, respectively. These results also suggest that an increase in the ratio of cAMP to cGMP is involved in the normal physiologic mechanism that promotes the onset of anaphase. If spontaneous increases in cyclic nucleotide levels at various points in the cell cycle are indicative of positive regulatory function, then cGMP may be involved in the modulation of some early events in mitosis and possibly in the S phase. (29 refs.)

- 77-7194 Frog Lysozyme. IV. Isozymes of Lysozyme and the Lucke Renal Adenocarcinoma. (Eng) Nace, G. W. (Div. Biological Sciences, 3103 Natural Science Building, Univ. Michigan, Ann Arbor, MI 48109); Ostrovsky, D. *J Natl Cancer Inst* 58(2): 453-454; 1977.

Lysozyme was extracted from Lucke renal adenocarcinomas obtained from five frogs (*Rana pipiens*), and the isozyme patterns were compared with those of normal frog kidney tissue (NK) using polyacrylamide gel electrophoresis. All 5 tumors contained isozyme No. 4, 4 contained No.7, 3 contained No. 2 contained No. 3, and only 1 contained No. 2. None of the tumors contained isozymes Nos. 5, 6, or 8, which were present with Nos. 1-4 and 7 in all NK extracts. The metabolic systems that regulate the synthesis of these isozymes are apparently different in tumor and NK tissue. The absence of lysozyme may be an important precondition for the infection of a frog kidney by an oncogenic herpesvirus. Also, the various forms of lysozymes may vary in their ability to inhibit virus. (9 refs.)

- 77-7195 The Undifferentiated Enzymic Composition of Human Fetal Lung and Pulmonary Tumors. (Eng) Greengard, O. (Dept. Biological Chemistry, Harvard Medical Sch., Boston, MA 02215); Herzfeld, A. *Cancer Res* 37(3): 884-891; 1977.

The concentrations of 16-21 enzymes representing various metabolic pathways were studied in human adult, fetal, and neoplastic lung, and the findings were compared with those for fetal and adult human liver and rat lung. A comparison of neoplastic tissue and midgestational fetal lung indicated that in each case, the same 12 enzymes (thymidine kinase, peptidyl proline hydroxylase, phosphoserine phosphatase, pyrroline-5-carboxylate reductase, pyrroline-5-carboxylate reductase [NEC, not exposed to cold], N⁵-methyltetrahydrofolate-homocysteine methyltransferase, glucose-6-phosphate dehydrogenase, hexosephosphate aminotransferase, glutamate dehydrogenase, aspartate aminotransferase, aspartate aminotransferase [Mt], ornithine aminotransferase, alanine aminotransferase) were elevated and the same (2 methylene hydrofolate reductase, dihydropyridine reductase) were decreased below normal adult tissues. Hexokinase was elevated in neoplastic tissue and depressed below normal in fetal lung; this could be due to the dedifferentiated nature of the tissue. The fetal and neoplastic tissues were not identical, however, in their enzymatic composition. The concentration of the various enzymes varied greatly among tumors and metastases. The best markers of neoplastic transformation were thymidine kinase, peptidyl proline hydroxylase, phosphoserine phosphatase, hexokinase, and pyrroline-5-carboxylate reductase. (34 refs.)

- 77-7196 Magnesium and Calcium Effects on Uptake of Hexoses and Uridine by Chick Embryo Fibroblasts. (Eng.) Bowen-Pope, D. F. (Dept. Molecular Biology, Univ. California, Berkeley, CA 94720); Rubin, H. *Proc Natl Acad Sci USA* 74(4): 1585-1589; 1977.

Secondary cultures of chick embryo fibroblasts were incubated in media containing different Ca²⁺ and Mg²⁺ concentrations. Cultures preincubated for 7 hr in 0.028 millim Mg²⁺ showed a ³H-uridine uptake at 24% of the rate for cultures preincubated in 0.8 millim Mg²⁺, indicating that Mg²⁺-sufficient cultures grew more rapidly. Mg²⁺ and Ca²⁺ deprivation, to a lesser degree, produced a decrease in the V_{max} of the glucose transport system for the D-glucose analogs 3-O-³H-methyl-D-glucose (³H-MeGlu) and 2-deoxy-D-³H-glucose (³H-dGlu) and a parallel decrease in lactate production. Readdition of Mg²⁺ to cultures deprived of Mg²⁺ resulted in a rapid increase in transport activity, even when protein synthesis was inhibited, and increased the rate of ³H-dGlu uptake without RNA synthesis. Ca²⁺ deprivation increased the leakiness of cells to the nontransported hexose L-³H-Glu, suggesting that Ca²⁺ is required to maintain the cell permeability barrier. The effect produced by Mg²⁺ deprivation was identical to

the effect of variables such as serum concentration and population density. (17 refs.)

- 77-7197 **Effect of the Ionophore A23187 upon Lymphocyte Calcium Metabolism.** (Eng.) Jensen, P. (Dept. Internal Medicine, Yale Univ. Sch. Medicine, New Haven, CT 06510); Rasmussen, H. In: *Regulatory Mechanisms in Lymphocyte Activation*. Lucas, D. O., ed. (New York: Academic Press, Inc.): 825 pp.; 438-440; 1977.

The addition of mitogenic concentrations of ionophore A23187 to freshly isolated human peripheral lymphocytes suspended in minimum essential medium plus 10% AB serum resulted in a new increase in lymphocyte Ca content. However, the increased Ca was not retained, and the content declined to control values over several hrs. This Ca accumulation appeared to be sequestered by mitochondria, because the respiratory uncoupler FCCP blocked at least 95% of the A23187-induced 45 Ca uptake. Evidence from three further experiments suggests that the biphasic nature of ionophore-induced Ca uptake was due to a redistribution with time of A23187 from the plasma membranes to the intracellular (including mitochondrial) membranes, where A23187 can act to cause a net Ca efflux. The time required was a function of A23187 concentration. The data are consistent with the hypothesis that an increase in Ca concentration is a critical signal in the initiation of lymphocyte proliferation. (6 refs.)

- 77-7198 **Glucocorticoid Receptors and Glucocorticoid Sensitivity of Mitogen Stimulated and Unstimulated Human Lymphocytes.** (Eng) Smith, K. A. (Dept. Medicine, Dartmouth Medical Sch., Hanover, NH 03755); Crabtree, G. R.; Kennedy, S. J.; Munck, A. U. *Nature* 267(5611): 523-526; 1977.

The inhibitory effects of glucocorticoids on metabolic parameters and the number of glucocorticoid receptors in cultured human lymphocytes undergoing transformation were measured simultaneously. Human lymphocytes were cultured and assayed with dexamethasone (DX) for nuclear glucocorticoid receptor sites. Following addition of concanavalin A (Con A) to the cultured lymphocytes, there was a sixfold increase in receptor sites per cell by 24 hr, with max levels occurring before 48 hr. In experiments with cells from 10 individuals, there was a two- to fourfold increase in DX binding sites per cell over unstimulated controls, regardless of the mitogenic stimulus. DX was added to lymphocytes after 24, 48, and 72 hr of culture in the presence of Con A, and the incorporation of 3 H-thymidine and 3 H-uridine was measured. DX suppressed the incorporation of both isotopes significantly, but it did not alter viable cell numbers. Thus, mitogen stimulation leads to a marked increase in the number of glucocorticoid receptors per cell, and the cells remain sensitive to glucocorticoids. The results suggest that in human lymphoid cells, receptor number may correlate with the pro-

liferative stage of the cell and may not determine glucocorticoid sensitivity. (13 refs.)

- 77-7199 **Polycythemia Vera: Hormonal Modulation of Erythropoiesis In Vitro.** (Eng) Golde, D. W. (Div. Hematology-Oncology, Dept. Medicine, Univ. California at Los Angeles Sch. Medicine, Los Angeles, CA 90024); Bersch, N.; Cline, M. J. *Blood* 49(3): 399-405; 1977.

The interaction of erythropoietin with RBC progenitors in polycythemia vera was examined in vitro. Bone marrow obtained from five patients with typical disease and five healthy controls was assayed for erythroid colony formation (CFU-E) by the methylcellulose technique. In cultures without added erythropoietin, the mean cloning efficiency of the polycythemia vera marrow was eightfold higher than that of normal marrow. There was prominent stimulation of colony formation by erythropoietin, and the shape of the erythropoietin dose-response curves appeared to be similar in both patients and controls. Antierythropoietin antibody reduced the number of CFU-E in cultures not containing added erythropoietin, but it did not eliminate them. Dexamethasone (10^{-9} M) caused a consistent increase in CFU-E in the patients' cultures. These studies provide evidence for functional erythropoietin and glucocorticosteroid receptor mechanisms on erythroid precursors in polycythemia vera. The observations are consistent with a concept of this disease as a disorder of hematopoietic stem cells in which peripheral erythrocytosis is caused by an expanded erythroid progenitor compartment that maintains responsiveness to hormonal modulation. (11 refs.)

- 77-7200 **Metabolism of Estrogens in Hepatomas of Different Growth Rates.** (Eng) Abul-Hajj, Y. J. (Coll. Pharmacy, Univ. Minnesota, Minneapolis, MN 55455); Morris, H. P. *Cancer Res* 37(4): 1083-1087; 1977.

Estrogen 16 α -hydroxylase (EH) activity was measured in nine Morris hepatomas of different growth rates and in host livers. In the hepatomas, microsomal EH activity decreased significantly with increase in hepatoma growth rate. The slow-growing hepatomas (44, 28A, and 9633) had 16%-19% of the enzyme activity of normal livers. The activity decreased to values of 2%-9% in the more rapidly growing hepatomas (38B, 7795, and 5123a) and to 0% in the fastest growing hepatomas (788, 7777, and 42A). EH activity in the liver microsomes of tumor-bearing rats was 66%-90% of that in control microsomes. The activity in the host liver did not correlate with tumor growth rate. Phenobarbital-stimulated EH activity increased fourfold in normal liver and only two- to threefold in host livers. The slow- and intermediate-growing hepatomas showed a 1.2- to 1.4-fold increase in enzyme activity, but no activity or stimulation was observed in the fast-growing hepatomas. (30 refs.)

Author Index

- Abbondandolo, A., 77-6772
 Abul-Hajj, Y. J., 77-7200
 Adam, E., 77-6870
 Aden, D. P., 77-7037, 77-7141
 Ajdukiewicz, A. B., 77-7160
 Albert, R. E., 77-6801
 Alexandrov, K., 77-6751
 Allegra, S., 77-7121
 Allen, J. R., 77-6814
 Allen, P. L., 77-7117
 Alonso, G., 77-6966
 Althoff, J., 77-6759, 77-6762, 77-6776
 Ambrose, K. R., 77-7045
 Ames, B. N., 77-6702
 Anderson, C. L., 77-7062
 Anderson, D. E., 77-7113, 77-7149
 Anderson, J., 77-7026
 Anderson, J. L., 77-7084
 Anderson, M. W., 77-6816
 Anderson, S., 77-7018
 Andersson-Anvret, M., 77-6998
 Andrusenko, V. A., 77-7166
 Anisimov, V. N., 77-6687
 Anonymus, 77-6616, 77-7173
 Anthony, P. P., 77-6989
 Aoki, S., 77-7163
 Arai, M., 77-6841
 Archer, M. C., 77-6763, 77-6777
 Archer, V. E., 77-6630
 Arcos, J. C., 77-6846
 Argus, M. F., 77-6846
 Arlett, C. F., 77-6903
 Arlinghaus, R. B., 77-6969
 Arnold, J., 77-6890, 77-6891
 Arnold, M., 77-6890, 77-6891
 Arsenyan, S. G., 77-6975
 Asselin, J., 77-6692, 77-6695, 77-6696
 Astier, A. M., 77-7091
 Atassi, G., 77-6691
 Atine, I., 77-6998
 Atl, B., 77-7130
 Au, W., 77-7137
 Au, W. W., 77-6785
 Augustin, A. A., 77-7067
 Aulakh, G. S., 77-6952
 Aune, S., 77-7103
 Autrup, H., 77-6727
 Auerbeck, D., 77-6896
 Aviles, D., 77-7140
 Axtell, L. M., 77-7152
 Azumi, J., 77-7127
 Bacalao, J., 77-6966, 77-6972
 Bachelier, L. T., 77-6977
 Baird, R., 77-6852
 Baird, W. M., 77-6729
 Bakayev, V. V., 77-7029
 Balan, I. V., 77-7166
 Balandin, I. G., 77-6949
 Baldwin, R. W., 77-6847
 Balis, M. E., 77-6789
 Ballinger, W., 77-6673
 Bandyopadhyay, A. K., 77-6953
 Bannasch, P., 77-6708, 77-6709
 Bannikov, G. A., 77-7109
 Barbason, H., 77-6766
 Bardawil, W. A., 77-7151
 Barker, L. F., 77-6989
 Barkla, D. H., 77-6857
 Barlow, J. J., 77-7115
 Barra, Y., 77-7091
 Barrett, L. A., 77-7107
 Barrows, G. H., 77-6866
 Barski, G., 77-6948
 Bartsch, H., 77-6607, 77-6721
 Bassir, O., 77-6671
 Bast, R. C., 77-6756
 Basuk, J., 77-6624
 Battula, N., 77-6923
 Bauer, F. L., 77-6864
 Baughman, K. L., 77-7135
 Baumgartener, L. E., 77-6938
 Bayley, A. C., 77-6989
 Bazin, H., 77-7143
 Beaufrand, M. J., 77-6715
 Becker, Y., 77-7001
 Beckers, A., 77-7143
 Beierwaltes, W. H., 77-6634
 Beliaeva, N. M., 77-6800
 Belitsky, G. A., 77-6731, 77-6739
 Bellomy, B. B., 77-7045
 Bencko, V., 77-6810
 Benda, P., 77-6784
 Bendall, R. D., 77-6682
 Beneke, J. S., 77-7004
 Beniashvili, D. Sh., 77-6780
 Benjamin, H. E., 77-7076
 Benson, H. G., 77-6791
 Berg, K., 77-7052
 Bergman, D. G., 77-7012
 Bern, H. A., 77-6875
 Bersch, N., 77-7199
 Betz, E. H., 77-6766, 77-6769
 Beug, H., 77-6915
 Bichler, K. H., 77-6840
 Biddison, W. E., 77-7049
 Bigaliev, A. V., 77-6803
 Bigner, D. D., 77-6957, 77-6958
 Bignon, J., 77-6912, 77-6913
 Bilger, L., 77-6801
 Billing, R., 77-7078
 Binder, G. L., 77-6870
 Binder, M., 77-7003
 Bingham, E. L., 77-6853
 Birg, F., 77-6978
 Bishop, J. M., 77-6919
 Bissell, M. J., 77-6931
 Blair, P. B., 77-7066
 Blakeslee, J. R., 77-7012
 Blau, G. E., 77-6606
 Block, M. A., 77-7119
 Bodnar, G. V., 77-7166
 Bogaars, H. A., 77-7122
 Boggs, D. R., 77-7133
 Boggs, S. S., 77-7133
 Bogovski, P., 77-6664
 Boh, E., 77-6799
 Bolognesi, C., 77-6850
 Bolognesi, D. P., 77-6957, 77-6958
 Bonatti, S., 77-6772
 Bond, V. P., 77-6631
 Boon, T., 77-7044
 Boone, C. W., 77-6935, 77-7083
 Borland, R., 77-6773
 Borzsonyi, M., 77-6786
 Bouck, N., 77-6858
 Boutwell, R. K., 77-6689, 77-6747
 Bowen-Pope, D. F., 77-7196
 Bowman, H. E., 77-7076
 Boyer, S. H., 77-7077, 77-7187
 Braatz, J. A., 77-7085
 Bracken, W., 77-6755
 Bracken, W. M., 77-6742
 Bragg, K. U., 77-7152
 Brambilla, G., 77-6850
 Branca, M., 77-6970
 Brand, I., 77-6910
 Brand, K. G., 77-6910, 77-7035
 Breeden, C. R., 77-6871
 Bresnick, E., 77-6722
 Brightwell, J., 77-6879
 Brill, E., 77-6839
 Bro-Jorgensen, K., 77-6944
 Brocklehurst, J. R., 77-6979
 Broder, S., 77-6649
 Bromley, P. A., 77-6924
 Brooks, S. C., 77-6865
 Bross, I., 77-7169
 Brown, I. V., 77-6688
 Brown, T. M., 77-7155
 Brozmanova, J., 77-6904
 Bryan, G. T., 77-7033
 Bryant, G. M., 77-6846
 Buchanan, R., 77-6894
 Buchler, D. A., 77-6892
 Buell, D. N., 77-6956
 Bullock, A. A., 77-7106
 Bundi, R. S., 77-6886
 Bundy, B. M., 77-7051
 Buoen, L. C., 77-6910, 77-7035
 Burch, J. C., 77-6873
 Burgaleta, C., 77-7128, 77-7132
 Burmester, B. R., 77-6918
 Burnett, W., 77-7161
 Burns, F. J., 77-6801
 Burton, R. C., 77-7046
 Busbee, D. L., 77-6757
 Byrd, B. F., 77-6873
 Cabrera-Juarez, E., 77-6907
 Cain, J. A., 77-6672
 Calabresi, P., 77-7122
 Calafat, J., 77-6933
 Calleman, C. J., 77-6824
 Calvin, M., 77-6725
 Cameron, D. A., 77-7039
 Cameron, R., 77-6658
 Campbell, J. G., 77-7124
 Campbell, R., 77-7182
 Campbell, T. C., 77-6614, 77-6670
 Campos, M. M., 77-7076

- Canaani, E., 77-6968
 Cannat, A., 77-7056
 Cannon, W. C., 77-6880
 Cantrell, E. T., 77-6757
 Cardiff, R. D., 77-6942
 Carmona, L., 77-6852
 Caron, M. G., 77-6695, 77-6696
 Carter, C. D., 77-7155
 Casto, B. C., 77-6793
 Catanzaro, P., 77-7146
 Cerutti, P., 77-6723
 Cerutti, P. A., 77-6724
 Ch'ih, J. J., 77-7184
 Chalopin, J. M., 77-7054
 Chan, C. H., 77-6989
 Chan, P., 77-7162
 Chandler, J. A., 77-7118
 Chang, C., 77-7084
 Chang, C. C., 77-6746
 Chang, R. L., 77-6699
 Chemeris, G. Iu., 77-6821
 Chern, C. J., 77-6729
 Chervenick, P. A., 77-7133
 Chi, D. S., 77-7063
 Chi, J., 77-6929
 Choppin, P. W., 77-7009
 Chou, C. C., 77-6669
 Christopher, J. P., 77-6837
 Christopherson, W. M., 77-6866
 Chrominska, H., 77-7172
 Chu, E. H., 77-6746
 Chumackov, P. M., 77-7029
 Clapp, M. J., 77-6703
 Clark, E. A., 77-7086
 Clark, T. D., 77-6955
 Claude, J. R., 77-6913
 Clay, J. E., 77-7171
 Cleaver, J. E., 77-6792
 Clemente, M. P., 77-7097
 Clifton, G., 77-6732
 Cline, M. J., 77-7128, 77-7199
 Clode, W. H., 77-7041
 Cloyd, M. W., 77-6957, 77-6958
 Coggin, J. H., 77-7045
 Cohen, L., 77-7162
 Cohen, S. M., 77-6657, 77-6841
 77-7033
 Cole, P., 77-6665, 77-7157
 Cole, P. T., 77-6620
 Coles, S., 77-7092
 Collier, P. F., 77-6825
 Collins, C. J., 77-6921
 Collins, J. K., 77-7024, 77-7027
 Coloma, J., 77-6677
 Colton, T., 77-7157
 Conard, R. A., 77-6882
 Conaway, C. C., 77-6822
 Condit, R. C., 77-6978
 Conley, C. L., 77-7135
 Connan, G., 77-6926
 Conney, A. H., 77-6699, 77-6722
 77-6742
 Conning, D. M., 77-6703
 Connor, R. J., 77-6905
 Conscience, J. F., 77-7187
 Constantinidis, K., 77-6627
 Conta, B. S., 77-7023
 Contreras, R., 77-7016
 Cooper, R. A., 77-7096
 Coppey, J., 77-7002
 Cornfield, J., 77-6605
 Correa, P., 77-7152
 Corti, G., 77-6772
 Cosenza, H., 77-7067
 Costlow, M. E., 77-6693
 Cotruvo, J. A., 77-6798
 Countryman, P. I., 77-6902
 Cowie, A., 77-6978
 Cowie, C. H., 77-6955
 Cox, R., 77-6790
 Crabtree, G. R., 77-7198
 Craig, J., 77-6682
 Craven, P. A., 77-6779
 Crawford, E., 77-6902
 Crittenden, L. B., 77-6918
 Croce, C. M., 77-7011
 Croisy, A., 77-6684
 Croisy-Delcey, M., 77-6684
 Crosby, W. H., 77-6613
 Cross, J. D., 77-7171
 Crouch, N. A., 77-6939
 Csik, M., 77-6786
 Cummings, F. J., 77-7122
 Cummins, S. D., 77-7106
 Cutler, L. S., 77-7102
 Czernielewska, I., 77-7172
 Daams, H., 77-6933
 Dagle, G. E., 77-6880
 Dalderup, L. M., 77-6623
 Dale, I., 77-7171
 Damsky, C. H., 77-6943
 Danes, B. S., 77-7105
 Danguy, A., 77-6691
 Dansette, P. M., 77-6751
 Darlix, J. L., 77-6924
 Dashman, T., 77-6717
 Daune, M. P., 77-6815
 Dayal, H., 77-7161
 de Man, J. C., 77-6990
 de Saint-Blanquat, G., 77-6716
 de-The, G., 77-6998, 77-7054
 de Weerd-Kastelein, E. A., 77-6903
 Debry, G., 77-6715
 Dedrick, R. L., 77-6816
 DeFlorio, D., 77-7121
 DeGroot, L. J., 77-6885
 Delotto, R., 77-7015
 DePamphilis, M. L., 77-7018
 DePhilip, R. M., 77-7190
 DePierre, J. W., 77-6753
 Derubertis, F. R., 77-6779
 Desai, D., 77-6820
 Devare, S. G., 77-7007
 Devlin, T. M., 77-7184
 Dexter, T. M., 77-6937
 Dhar, R., 77-7017
 Diamond, I., 77-7122
 Diamond, L., 77-6729, 77-6744, 77-6748
 Diaz-Gil, J., 77-6677
 Dickson, C., 77-6940
 Dikun, P. P., 77-6733
 Dil'man, V. M., 77-6687
 DiMayorca, G., 77-6858
 Dina, D., 77-6968
 Dingemans, K. P., 77-7125
 Dinowitz, M., 77-6930
 DiPaolo, J. A., 77-6793
 Dismukes, W. E., 77-7123
 Dmitriev, V. N., 77-6806
 Dmitrievskaia, A. Iu., 77-6687
 Dobyns, B. M., 77-6632
 Dodi, G., 77-6673
 Doerr, R. C., 77-6718
 Dolken, G., 77-6995
 Dombrowski, P., 77-7032
 Dominiczak, K., 77-6812
 Doniach, I., 77-6635
 Dooley, K., 77-6871
 Dostal, V., 77-7003
 Douglas, J. F., 77-6604
 Dover, G. J., 77-7077
 Drevon, C., 77-6770
 Drill, V. A., 77-6866
 Driscoll, D. M., 77-6938
 Ducean, B. W., 77-6678
 Duesberg, P., 77-6968
 Dulbecco, R., 77-6979
 Durm, M., 77-6649
 Dutkiewicz, T., 77-6809
 Eagan, J. W., 77-7135
 Ebert, P. S., 77-6956
 Economou, G. C., 77-7083
 Edington, G. M., 77-7160
 Eggleston, J. C., 77-7135
 Ehrenberg, L., 77-6824
 Eichwald, E. J., 77-6905
 El'tsina, N. V., 77-6619
 Elder, J. H., 77-6965
 Elemesova, M. Sh., 77-6803
 Eling, T. E., 77-6816
 Emanuel, N. M., 77-6950
 Emerole, G. O., 77-6671
 Emery, S., 77-6964
 Epstein, M. A., 77-6996
 Epstein, S. S., 77-6741
 Erikson, E., 77-6922
 Erikson, R. L., 77-6922
 Erizer, T. L., 77-6739
 Ernster, L., 77-6753
 Ershov, F. I., 77-6638
 Erskine, J. G., 77-7126
 Essex, M., 77-6641, 77-6934
 Evans, F. J., 77-6749
 Evans, J. T., 77-6855
 Extremet, J., 77-6908
 Ezrin, C., 77-7120
 Fakunle, Y. M., 77-7160
 Faller, D. V., 77-6946
 Farber, E., 77-6658, 77-7108
 Farmer, J. H., 77-6867
 Farson, D., 77-6931
 Favus, M. J., 77-6890, 77-6891
 Fears, T. R., 77-6604
 Feaux de Lacroix, W., 77-7175
 Fedosov, E. A., 77-7038
 Feldman, S., 77-6673
 Ferguson, J. A., 77-7076
 Ferrando, R., 77-6868

- Fialkow, P. J., 77-7119
 Fichidzhian, B. S., 77-6819
 Fiddler, W., 77-6718
 Fiers, W., 77-7016
 Finerty, S., 77-6996
 Fink, D., 77-6915
 Finkle, W. D., 77-6874
 Fiorio, R., 77-6772
 Fischinger, P. J., 77-6969
 Flake, R. E., 77-6827
 Flaks, A., 77-6697, 77-6872
 Fleming, N., 77-6700
 Fowler, B. A., 77-6811
 Fox, A. J., 77-6825
 Foy, H., 77-6666
 Frank, N., 77-6767
 Franks, L. M., 77-6686
 Fraumeni, J. F., 77-7156
 Frayssinet, C., 77-6751
 Freeman, A. E., 77-6740
 Freeman, K. B., 77-6829
 Frenkel, J. K., 77-7061
 Fresco, R., 77-6908
 Fresen, K. O., 77-6994
 Fridman-Manduzio, A., 77-6766
 77-6769
 Fried, J., 77-7179
 Friedell, G. H., 77-6657, 77-6841
 Friedman, B., 77-7006
 Friend, C., 77-7187
 Frigg, M., 77-6685
 Fritsch, P., 77-6716
 Frohman, L. A., 77-6890, 77-6891
 Fry, R. J., 77-6837
 Fu, P. P., 77-6698
 Fuchs, R. P., 77-6815
 Fujinaga, K., 77-6988
 Fujita, D. J., 77-6919
 Fuller, C. R., 77-7075
 Gaas, G. H., 77-6871
 Gaconnet, N., 77-6715
 Gaines, J. A., 77-7032
 Gallo, R. C., 77-6642, 77-6952, 77-7006
 Gammon, M., 77-6980
 Gangolli, S. D., 77-6774, 77-6775
 Gardner, D. G., 77-7101
 Garibian, D. Kh., 77-6819
 Garrido, F., 77-7090
 Gates, F. T., 77-6906
 Gautsch, J. W., 77-6965
 Gavora, J. S., 77-7089
 Gay, P. C., 77-6827
 Geacintov, N. E., 77-6735
 Geddes-Dwyer, V., 77-7039
 Gedigk, P., 77-6713
 Gehring, P. J., 77-6606, 77-6826
 Gelboin, H., 77-6719
 Gelboin, H. V., 77-6727, 77-6756
 Georgiev, G. P., 77-7029
 Gerber, P., 77-6644
 Gerety, R. J., 77-6989
 Gericke, D., 77-6840
 Gershman, S. T., 77-6633
 Gershwin, M. E., 77-7036
 Gervais, F., 77-6991
 Gibson, R., 77-7161
 Gillette, R. W., 77-7081
 Gilson, J. C., 77-6628
 Giovanella, B. C., 77-6996
 Gisselbrecht, S., 77-7056
 Glazer, R. I., 77-6832
 Glick, M. C., 77-6971
 Glusker, J. P., 77-6698
 Gluzman, Y., 77-7020, 77-7021
 Gol-Winkler, R., 77-6769
 Goldberg, N. D., 77-7193
 Golde, D. W., 77-7128, 77-7132
 77-7199
 Goldfeder, A., 77-7178
 Goldman, C., 77-6649
 Golomb, H. M., 77-6659
 Goloshchapov, P. V., 77-6884
 Gopalakrishnan, T. V., 77-7191
 Gorby, D. R., 77-6720
 Gordon, J., 77-6874, 77-7079
 Gosalvez, M., 77-6677
 Gothe, R., 77-6824
 Gothoskar, S. V., 77-6681
 Goutier, R., 77-6769
 Grab, D. J., 77-6862, 77-6863
 Gracheva, G. M., 77-6687
 Graf, T., 77-6915
 Graham, S., 77-7161
 Grandjean, C., 77-6759, 77-6776
 Grasso, P., 77-6775
 Gray, P. M., 77-6870
 Greenawald, K. A., 77-7119
 Greene, M. H., 77-7156
 Greengard, O., 77-7195
 Greenman, D. L., 77-6871
 Greenwood, B. M., 77-7160
 Grey, H. M., 77-7062
 Griffith, K., 77-7032
 Grim, C. E., 77-7112
 Grinberg, K. N., 77-6739
 Grinwich, K., 77-7030
 Gross, R. L., 77-6612
 Grottsch, H., 77-6840
 Grover, P. L., 77-6721
 Grufferman, S., 77-7153
 Grundmann, E., 77-6710
 Gudim-Levkovitch, K. A., 77-6680
 Guelstein, V. I., 77-7109
 Guerin, M. R., 77-6701
 Guerry, R., 77-6751
 Guimard, J., 77-6704
 Guirgis, H. A., 77-6661, 77-7150
 77-7151
 Gupta, P., 77-7000
 Gushchin, V. A., 77-7174
 Gutierrez, A. C., 77-7169
 Gutmann, H. R., 77-6834
 Haahr, S., 77-7053
 Haapala, D. K., 77-6969
 Haas, M., 77-6962
 Hacker, H. J., 77-6708
 Hadjiolov, D., 77-6767
 Hakomori, S., 77-7057
 Hale, A. H., 77-6925
 Hall-Smith, P., 77-6903
 Halnan, K. E., 77-6886
 Hamburger, J. I., 77-6887
 Hamilton, J. M., 77-6872
 Hamman, J. P., 77-6720
 Hanafusa, H., 77-6918
 Hanausek-Walaszek, M., 77-6788
 Handa, H., 77-6986
 Handleman, S. L., 77-7145
 Hann, W. D., 77-6999
 Haran-Ghera, N., 77-7088
 Harcourt, S. A., 77-6903
 Hard, G. C., 77-6773
 Hardesty, B., 77-7188
 Harding, M., 77-7019, 77-7139
 Hardy, W. D., 77-6640, 77-6641
 77-6934
 Harmon, R. C., 77-7086
 Harnden, D. G., 77-7019
 Harris, C. C., 77-6727, 77-7107
 Harris, J., 77-6647, 77-6856
 Harris, N. S., 77-7063
 Harris, R. E., 77-6661, 77-7150
 77-7151
 Hartley, J. W., 77-6965
 Harvey, R. G., 77-6698
 Harzmann, R., 77-6840
 Hauschka, T. S., 77-6855
 Havrankova, H., 77-6810
 Haworth, S. R., 77-6795
 Hayes, A. A., 77-6640, 77-6934
 Hayes, A. W., 77-6672
 Hayes, D., 77-7110
 Hayes, J. R., 77-6670
 Hayman, E. G., 77-6920
 Hays, E. F., 77-6963
 Heading, C. E., 77-6774
 Headley, D. B., 77-7033
 Hearst, J. E., 77-7025
 Heath, C. W., 77-7155
 Hecht, S. S., 77-6706, 77-6707
 Heddle, J. A., 77-6902
 Hellman, S., 77-7114
 Hempelmann, L. H., 77-6888
 Henle, G., 77-7055
 Henle, W., 77-6645, 77-6998, 77-7055
 Hensen, F. J., 77-7175
 Heppleston, A. G., 77-6879
 Herberman, R. B., 77-7050, 77-7085
 77-7176
 Herbert, J. T., 77-7155
 Herbst, A. L., 77-7157
 Herha, J., 77-6610
 Herman, K., 77-6737
 Heron, I., 77-7052, 77-7053
 Hersey, P., 77-7039
 Herzfeld, A., 77-7195
 Hess, P. W., 77-6640
 Heuson, J. C., 77-6691
 Heuson-Stiennon, J., 77-6691
 Heusser, C. H., 77-7062
 Hiai, H., 77-6945
 Hicks, R. M., 77-6783
 Highman, B., 77-6867
 Hildemann, W. H., 77-7086
 Hilfrich, J., 77-6706
 Hill, P., 77-7162
 Hinze, H. C., 77-6939
 Hirai, K., 77-7013

- Hirshberg, G., 77-6673
Ho, I. K., 77-6820
Ho, J. H., 77-7054
Hodges, G. M., 77-6783
Hoffmann, D., 77-6706
Holden, H. T., 77-7176
Holtzer, H., 77-6745
Hoover, E. A., 77-7082
Hoover, R., 77-7156
Hopkins, G. J., 77-6676
Hopkins, N., 77-6946
Hopp, M. L., 77-6836
Horm, J. W., 77-7148
Horne, C. H., 77-7180
Horton, A. W., 77-6853
Horvath, E., 77-7120
Houseman, T. H., 77-6817
Houten, L., 77-7169
Howe, M. L., 77-7070
Howk, R., 77-6959
Howley, P. M., 77-6982
Huang, C. C., 77-7069
Hue, G., 77-6948
Huebner, R., 77-7043
Hughes, R. C., 77-7181
Huiskens-v. d. Meij, J. W., 77-6990
Hultmark, D., 77-6824
Hunter, B., 77-6791
Hunter, I. W., 77-7110
Hutt, L. M., 77-7121
Hutton, M. M., 77-7126
Hyde, R. T., 77-7154
Hyland, C. H., 77-7123
Hyland, J., 77-7010
Iakovleva, L. S., 77-7042
Igbal, Z. M., 77-6741
Igel, H. J., 77-6740
Ihle, J. N., 77-7043
Ikeda, R. M., 77-7036
Il'in, A. P., 77-6687
Il'in, K. V., 77-7005
Incze, J. S., 77-7097
Indo, K., 77-6734
Inui, N., 77-6842
Irriguible, M. D., 77-7131
Irving, C. C., 77-6790
Ishak, K. G., 77-7106
Ishiwata, H., 77-6778
Ishiwata, K., 77-7094
Itabashi, M., 77-6845
Ito, N., 77-6714
Ito, Y., 77-6979
Itzhaki, M., 77-7068
Ivanov-Golitsyn, M. N., 77-6733
Iwasaki, Y., 77-7141
Jackson, C. E., 77-7119
Jackson, S. F., 77-6829
Jacob, H. S., 77-7185
Jacobs, J. B., 77-6657, 77-6841
Jacquignon, P., 77-6684
Jain, S. C., 77-6851
Jami, J., 77-7140
Janosko, N., 77-6793
Jaurand, A. C., 77-6912
Jaurand, M. C., 77-6913
Jenkins, R. L., 77-6852
Jensen, E. M., 77-6795
Jensen, F. C., 77-6965
Jensen, N. M., 77-6752
Jensen, P., 77-7197
Jerina, D., 77-6723
Jerina, D. M., 77-6699, 77-6722
77-6742
Jerry, L. M., 77-7079
Johannesen, K. A., 77-6753
Johnson, E. F., 77-6813
Johnson, I. J., 77-6828
Joishy, S. K., 77-7096
Joncas, J., 77-6991
Jones, F. L., 77-7093
Jones, G. M., 77-7145
Jones, L. A., 77-6875
Jones, R. T., 77-7107
Jones, S. E., 77-7032
Jubert, A. V., 77-7076
Julia, A., 77-7131
Julius, M. H., 77-7067
Kaddu-Mukasa, A., 77-6998
Kaji, A., 77-6928, 77-6929, 77-7015
Kalderon, A. E., 77-7122
Kalistratova, V. S., 77-6883
Kamen, R., 77-6978
Kamm, J. J., 77-6717
Kanzaki, T., 77-6869
Kaplan, J., 77-7074
Kaplan, S. R., 77-7122
Kaplowitz, N., 77-6732
Karle, J. M., 77-6699
Karnovsky, M. J., 77-7182
Kaschula, V. R., 77-7008
Kashmiri, S. V., 77-7013
Kasprzak, K. S., 77-6807
Kataoka, T., 77-7040
Kaufman, R. H., 77-6870
Kaufmann, G., 77-7018
Kawachi, T., 77-6714, 77-6802
Kawaguchi, T., 77-7136
Kawai, S., 77-6919
Kawakami, T. G., 77-7036
Kay, A. C., 77-7014
Kazazian, H. H., 77-7077
Keijzer, W., 77-6903
Kelleher, P. C., 77-6848
Keller, J. M., 77-6973
Kellermann, O., 77-7044
Kelley, P. A., 77-6695
Kelly, P. A., 77-6692, 77-6696
Kemp, J. D., 77-7186
Kennedy, A. R., 77-6736
Kennedy, J. R., 77-7117
Kennedy, S. J., 77-7198
Kennel, S. J., 77-6961
Kent, D. R., 77-7159
Kent, E., 77-6911
Khar'kovskaia, N. A., 77-6838
Khesina, A. Ya., 77-6739
Khiroya, R., 77-6945
Khrustalev, S. A., 77-6838
Kilian, D. J., 77-6827
Kimoto, T., 77-6861
Kinoshita, I., 77-7104
Kirby, P. E., 77-6795
Kirk-Bell, S., 77-6903
Kiselev, F. L., 77-6975
Kiseleva, N. S., 77-6794
Kistler, G. S., 77-6700
Klaiber, M., 77-7108
Klassen, R., 77-6682
Klein, D., 77-6715
Klein, G., 77-6993, 77-6995, 77-6998
77-7087
Klein, P. J., 77-7175
Kleinerman, J., 77-7146
Klimashevskii, V. F., 77-7174
Kline, J., 77-6625
Klochko, A. V., 77-6950
Klochko, E. V., 77-6950
Knowles, B. B., 77-7037
Knowles, M. A., 77-6686
Knowlton, R. P., 77-7073
Knudson, A. G., 77-6660
Knudtzon, S., 77-6944
Koblyakov, V. A., 77-6731
Kobori, O., 77-6713
Koestner, A., 77-7142
Koestner, A. W., 77-7142
Kolodin, V. I., 77-6897
Kominami, S., 77-6900
Koons, L. S., 77-7073
Kopelovich, L., 77-6652, 77-6974
Koppel, H., 77-6981
Korosteleva, T. A., 77-6843
Kosuge, T., 77-6802
Kovacs, K., 77-7120
Kovi, E., 77-6849
Kovi, J., 77-6849
Kozhevnikova, E. P., 77-6800
Krakauer, R., 77-6649
Kramer, G., 77-7188
Kripke, M. L., 77-6637, 77-6905
Kriukova, I. N., 77-7005
Kropko, M. L., 77-6740
Krugliakova, K. E., 77-6950
Krush, A. J., 77-7105
Krutchkoff, D., 77-7102
Krzywanska, E., 77-6728
Kuff, E. L., 77-7020
Kuga, N., 77-6976
Kumaki, K., 77-6752
Kuno, K., 77-7162
Kupper, R., 77-6854
Kuroki, T., 77-6721, 77-6770
Labrie, F., 77-6692, 77-6695, 77-6696
Lacy, P., 77-6673
Lafarge-Frayssinet, C., 77-6751
Lai, C. J., 77-7024
Lai, M. M., 77-6920
Laishes, B., 77-6658
Lake, B. G., 77-6774, 77-6775
Lake, R. S., 77-6740
Lalich, J. J., 77-6814
Lam, K. W., 77-7134
Lam, L. K., 77-6730
Lamb, R. A., 77-7009
Lamelin, J. P., 77-7054
Lamki, H., 77-7110
Lane, B. P., 77-6688
Lane, W. W., 77-7169

- Lang, M. C., 77-6815
 Lapointe, N., 77-6991
 LaPolla, R. J., 77-6795
 Laskey, R. A., 77-7028
 Latarjet, R., 77-6896
 Layard, M., 77-6911
 Ledbetter, J., 77-6947, 77-6964
 Lee, C., 77-6836
 Lee, J. C., 77-7043
 Lee, J. J., 77-6917
 Lee, R. E., 77-7133
 Lee, S. G., 77-6927
 Lee, Y. N., 77-6651
 Leffler, S., 77-6835
 Legros, N., 77-6691
 Lehmann, A. R., 77-6903
 Lehmann, F. G., 77-6621
 Lehr, R. E., 77-6699
 Lelievre, P., 77-6766
 Lemon, H. M., 77-6617, 77-6618
 Lennartz, K. J., 77-7175
 Leonard, E. J., 77-7059
 Leonard, T. B., 77-6678
 Lerner, A. B., 77-6636
 Lerner, R. A., 77-6965
 Letnansky, K., 77-7003
 Levey, G. S., 77-6781
 Levin, W., 77-6699, 77-6722, 77-6742
 Levine, P. H., 77-6644
 Levinson, B. B., 77-7147
 Levy, C. C., 77-6953
 Levy, S., 77-6784
 Leyritz, M., 77-6991
 Li, L. H., 77-6955
 Lieberman, I., 77-7190
 Likhachev, A. Ia., 77-6733, 77-6897
 Lingwood, C. A., 77-7057
 Linker-Israeli, M., 77-7068
 Linn, S., 77-6906
 Linney, E., 77-7147
 Liotta, L. A., 77-7146
 Lipkin, M., 77-6652
 Lipmann, F., 77-6927
 Little, J. B., 77-6736
 Litwin, S. D., 77-7064
 Livingston, D. M., 77-7026
 Ijungquist, S., 77-6675
 Lloyd, A. G., 77-6775
 Loeb, L. A., 77-6916
 Logue, M. J., 77-7075
 Lok, E., 77-6804
 Lombard, M. N., 77-7111
 Lonai, P., 77-7088
 Longenecker, B. M., 77-7089
 Lopatin, D. E., 77-6648
 Loprieno, N., 77-6772
 Lorentzen, R. J., 77-6726
 Losasso, L., 77-6925
 Lovenetsky, A. N., 77-6975
 Lowery, L. T., 77-7081
 Lowy, D., 77-6959
 Lu, P. Y., 77-6796
 Luftig, R. B., 77-6985
 Lui, P. S., 77-7097
 Luka, J., 77-6993
 Lukshin, Iu. V., 77-6950
 Lutz, R. J., 77-6816
 Lynch, H. T., 77-6661, 77-7150
 77-7151
 Lynch, J. F., 77-7150, 77-7151
 Lynch, P. M., 77-7150, 77-7151
 Lynch, W. E., 77-7190
 MacEwen, E. G., 77-6640, 77-6934
 Macgregor, J. T., 77-6828
 MacKeigan, J. M., 77-7076
 Madhukar, B. V., 77-6822
 Mackawa, A., 77-6778
 Magne, L., 77-6912
 Magrath, I. T., 77-6644
 Mahaffey, K. R., 77-6811
 Maizel, J. V., 77-6987
 Majeski, J. A., 77-7058
 Maki, T., 77-7070
 Malaveille, C., 77-6721
 Malejka-Giganti, D., 77-6834
 Malherbe, H., 77-7008
 Malloy, E., 77-7133
 Malt, R. A., 77-6864
 Mancuso, T. F., 77-7170
 Mandel, D., 77-6796
 Mandybur, T. I., 77-7137
 Manni, A., 77-6694
 Marck, A., 77-7114
 Marcus, S. L., 77-6951, 77-6954
 Mardiney, M. R., 77-6953
 Margolet, L., 77-7187
 Markovits, P., 77-6784, 77-6896
 Marks, F., 77-6743
 Marks, P. A., 77-7179
 Marquardt, H., 77-6608, 77-6608
 Marsh, S., 77-6759, 77-6776
 Marth, E. H., 77-6669
 Martin, M. A., 77-6982
 Martin, R. G., 77-7026, 77-7084
 Martin, R. R., 77-6757
 Maruchi, N., 77-7163
 Maschio, F. A., 77-6789
 Masek, F., 77-6904
 Mason, T., 77-7168
 Mastromarino, A., 77-7164
 Matchin, G. A., 77-6800
 Matsukura, N., 77-6714
 Matsumoto, M., 77-6836
 Matsumoto, N., 77-7185
 Matsumoto, T., 77-6802
 Matsumura, F., 77-6822
 Matthay, R. A., 77-6895
 Matthews, H. B., 77-6816
 May, M., 77-6911
 Mayer, D., 77-6709
 Mazier, W. P., 77-7076
 Mazurenko, N. P., 77-7042
 Mazzaccaro, A., 77-6772
 Mbaya, V., 77-6666
 McCalla, D. R., 77-6829
 McCarter, J. A., 77-6967
 McClelland, A. J., 77-6640
 McCoy, E. C., 77-6831
 McCulloch, E. A., 77-7177
 McCullough, B., 77-6877
 McDonald, T. F., 77-6722
 McGandy, R. B., 77-6736
 McGrath, M., 77-6917
 McGuire, W. L., 77-6693
 McIntire, K. R., 77-7085
 McLemore, T. L., 77-6757
 McNicol, M. W., 77-6758
 Meade, B., 77-6649
 Meager, A., 77-7181
 Medline, A., 77-6658
 Medve, F., 77-6737
 Meehan, T., 77-6725
 Mehendale, H. M., 77-6820
 Meier, D. M., 77-6880
 Meisler, A. I., 77-7023
 Meissner, H. C., 77-6987
 Mekler, L. B., 77-6654
 Melman, A., 77-7112
 Meltzer, M. S., 77-7059
 Meneghini, R., 77-6667
 Mercier, M. J., 77-6833
 Mergens, W. J., 77-6717
 Metcalf, R. L., 77-6796
 Meyer, G., 77-6908, 77-7091
 Meyer, J., 77-6987
 Meyer, W., 77-6656
 Meyn, M. S., 77-6674, 77-6808
 Meyrick, B., 77-6662
 Michelich, V. J., 77-7035
 Migliozi, J. A., 77-6679
 Mikulski, T., 77-6812
 Milievskaja, I. L., 77-6794
 Miller, E., 77-6911
 Miller, S., 77-7135
 Mills, A. D., 77-7028
 Milsow, L., 77-7100
 Ming, P. M., 77-7010
 Mirvish, S. S., 77-6707, 77-6764
 Mishra, N., 77-6858
 Mitchell, M. S., 77-6895
 Mittleman, A., 77-6855
 Miyazawa, T., 77-7144
 Mizusaki, S., 77-6802
 Mochizuki, Y., 77-6845
 Modak, M. J., 77-6951, 77-6954
 Moldow, C. F., 77-6917
 Moller-Larsen, A., 77-7052, 77-7053
 Moller, W., 77-6735
 Montesano, R., 77-6770
 Moore, B. G., 77-6672
 Moore, C. J., 77-6690
 Mora, P. T., 77-7084
 Mori, T., 77-7116
 Moriame, M., 77-7143
 Moron, M. S., 77-6753
 Morris, H. P., 77-6849, 77-7200
 Morris, N. R., 77-7028
 Morrissey, P., 77-6945
 Moskalev, Iu. I., 77-6883
 Mouly, H., 77-7111
 Moustacchi, E., 77-6896
 Mozer, B. J., 77-6909
 Mufson, R. A., 77-6747
 Muldoon, J. P., 77-7076
 Mullen, Y., 77-7086
 Muller-Eberhard, U., 77-6813
 Munck, A. U., 77-7198
 Murad, T. M., 77-7123

- Murty, C. N., 77-6668
 Muto, M., 77-6928, 77-6929
 Myers, M. H., 77-7152
 Myren, J., 77-7103
 Nace, G. W., 77-7194
 Nadasdi, L., 77-6786
 Nadol, J. B., 77-6997
 Nagao, M., 77-6802
 Nagel, D., 77-6762, 77-6854
 Nagy, G. K., 77-6657
 Nairn, R., 77-7181
 Nakada, K., 77-7104
 Nakamura, K., 77-7136
 Namba, M., 77-6861
 Napalkov, N. P., 77-6897
 Naso, R. B., 77-6969
 Nathans, D., 77-7024
 Nazerian, K., 77-7065
 Nebert, D. W., 77-6752
 Nedospasov, S. A., 77-7029
 Nelson, D. L., 77-7051
 Nemoto, N., 77-6719
 Newberne, P. M., 77-6612
 Newell, N., 77-7008
 Newmark, H., 77-6717
 Nezelof, C., 77-7111
 Ng, A. K., 77-7085
 Nichols, A., 77-6624
 Nicoletti, L., 77-6970
 Nishi, Y., 77-6842
 Nishikubo, K., 77-7104
 Nishitani, K., 77-6861
 Nishizumi, M., 77-6801
 Nissen, E. D., 77-7159
 Nissen, S. E., 77-7159
 Nitchuk, W. M., 77-6877
 Noble, R. L., 77-6876
 Nocentini, S., 77-6784
 Nola, E., 77-7175
 Nomura, T., 77-6860, 77-6869
 Nordlund, J. J., 77-6636
 Normann, S. J., 77-7060
 Norvell, M. J., 77-6867
 Nowinski, R. C., 77-6947, 77-6964
 Nozawa, R. T., 77-7183
 Nudel, U., 77-7179
 Nunn, M. E., 77-7050
 O'Brian, T. G., 77-6748
 O'Brien, S. J., 77-6935
 O'Brien, T. G., 77-6744
 O'Connor, G. T., 77-7152
 Obe, G., 77-6610
 Oblin, A., 77-6913
 Oboshi, S., 77-6976
 Oda, T., 77-7189
 Odashima, S., 77-6778
 Ogawa, K., 77-6658
 Oh-hash, F., 77-7040
 Ohashi, I., 77-7104
 Ohta, H., 77-7104
 Okasinski, G. F., 77-6936
 Okayama, M., 77-6928, 77-6929
 Okazaki, W., 77-6918
 Okigaki, T., 77-6859
 Okuda, T., 77-6756
 Okun, J. D., 77-6763
 Ol'khovskaia, I. G., 77-7099
 Oldham, R. K., 77-7176
 Olsen, R. G., 77-7082
 Olson, C., 77-6938
 Olweny, C. L., 77-6998
 Orringer, E. P., 77-7075
 Ortaldo, J. R., 77-7176
 Oshimura, M., 77-7129
 Oskarsson, M. K., 77-6969
 Osnes, M., 77-7103
 Osterman-Golkar, S., 77-6824
 Ostretsova, I. B., 77-6823
 Ostrovsky, D. S., 77-7194
 Owens, I. S., 77-6754
 Owens, R. B., 77-7036
 Owor, R., 77-6998
 Oyasu, R., 77-6836
 Ozer, H. L., 77-7024
 Pacifici, M., 77-6745
 Padgett, B. L., 77-6983, 77-6984
 Paffenbarger, R. S., 77-7154
 Page, N. P., 77-6603
 Pal, B. K., 77-6920
 Palmer, J. C., 77-7049
 Pan, J., 77-7017
 Paolini, N. S., 77-6855
 Papac, R. J., 77-6895
 Papadopoulos, D., 77-6784
 Parfenova, T. M., 77-6949
 Park, J. Y., 77-7050
 Park, K. K., 77-6777
 Parodi, S., 77-6850
 Parrott, D. M., 77-7080
 Parsons, J. T., 77-6921
 Pasteels, J. L., 77-6691
 Patricio, M. B., 77-7041
 Pavlenko-Mikhailov, Iu. N., 77-6899
 Pazderka, F., 77-7089
 Pearson, G. R., 77-7004
 Pearson, J., 77-6688
 Pearson, O. H., 77-6694
 Pegg, A. E., 77-6771
 Peluso, R. W., 77-7009
 Peraino, C., 77-6837
 Peterson, W. D., 77-7074
 Pezzutti, M. R., 77-6740
 Pfeffer, L., 77-6652
 Pfeffer, L. M., 77-6974
 Phillips, J. C., 77-6774, 77-6775
 Picciano, D. J., 77-6827
 Pickren, J. W., 77-7169
 Piekarski, L., 77-6728
 Pierrepont, C. G., 77-7118
 Pietropaolo, C., 77-6971
 Pinney, D. J., 77-7077
 Pinphanichakarn, P., 77-7188
 Pinter, A., 77-6786
 Piver, M. S., 77-7115
 Plescia, A. M., 77-7030
 Plescia, O. J., 77-7030
 Plotkin, E., 77-6756
 Plummer, N., 77-6796
 Podolsky, D. K., 77-6980
 Pogosova, A. M., 77-6819
 Polan, C. E., 77-6670
 Popov, D. K., 77-6878
 Popova, N. V., 77-6844
 Popper, H., 77-6622
 Portaro, J., 77-7071
 Portis, J., 77-7072
 Potmesil, M., 77-7178
 Pour, P., 77-6759, 77-6762, 77-6776
 Powers, G. J., 77-6880
 Pozdeev, V. K., 77-6687
 Pozharisskii, K. M., 77-7174
 Price, M. R., 77-6847
 Pride, G. L., 77-6892
 Procyk, R., 77-7184
 Pugh-Humphreys, R. G., 77-7180
 Pullinger, D. H., 77-6817
 Purchase, H. G., 77-6918, 77-6992
 Purchio, A. F., 77-6922
 Purde, M., 77-6664
 Purtilo, D. T., 77-7121
 Putong, P., 77-7141
 Rabotti, G. F., 77-6926
 Raffetto, G., 77-6850
 Rahu, M., 77-6664
 Rakhu, M. A., 77-7165
 Randalu, K. Kh., 77-6782
 Ranney, D. F., 77-6648
 Rapp, F., 77-7000
 Rasmussen, H., 77-7197
 Ravindranath, Y., 77-7074
 Raynaud, J. P., 77-6692, 77-6695
 77-6696
 Razzouk, C., 77-6833
 Reagan, J. W., 77-6874
 Reddy, A. L., 77-7086
 Reddy, B. S., 77-6712, 77-6797
 77-7164
 Reddy, J. K., 77-7061
 Regan, J. D., 77-6858
 Reid, M., 77-6668
 Reiss-Gutfreund, R. J., 77-7003
 Reissig, M., 77-7008
 Remsen, J., 77-6723
 Renis, H. E., 77-6955
 Renner, H., 77-6898
 Revillard, J. P., 77-7054
 Reynolds, F. H., 77-7007
 Reynolds, R. K., 77-7007
 Ricardo, J. A., 77-7041
 Rich, R. R., 77-6650
 Rich, S. S., 77-6650
 Richie, R. C., 77-6757
 Rieber, M., 77-6966, 77-6966, 77-6972
 77-6972
 Riesz, P., 77-6900
 Rifkind, R. A., 77-7179
 Rinehart, K. L., 77-6955
 Ringold, G. M., 77-6941, 77-6942
 Ristow, H. J., 77-6610
 Ritz, E., 77-7140
 Robboy, S. J., 77-7157
 Roberfroid, M., 77-6833
 Robey, W. G., 77-6969
 Rode, H. N., 77-7079
 Roessner, A., 77-6710, 77-6711
 Rogers, A. E., 77-6765
 Rogers, C. M., 77-6984
 Rogiers, R., 77-7016

- Romsdahl, M. M., 77-7149
 Roos, E., 77-7125
 Rose, F. L., 77-6738
 Rosen, F. S., 77-6646
 Rosenberg, S. A., 77-7031
 Rosenkranz, H. S., 77-6831
 Ross, A. E., 77-6764
 Rossman, T., 77-6674
 Rossman, T. G., 77-6808
 Rossner, P., 77-6810
 Roth, S., 77-6929
 Roth, S. L., 77-7015
 Roubinian, J. R., 77-7066
 Roudebush, C. P., 77-6885
 Rousseau-Merck, M. F., 77-7111
 Rousset, J. P., 77-7140
 Rovera, G., 77-6748, 77-7010
 Rovere, L. E., 77-6781
 Rowden, G., 77-7079
 Rowe, W. P., 77-6965
 Rowley, J. D., 77-6659
 Rowley, P. T., 77-7096
 Roy-Burman, P., 77-6920
 Royer-Pokora, B., 77-6915
 Rubenchik, B. L., 77-6611
 Rubin, H., 77-7196
 Rubin, I. B., 77-6701
 Ruddie, F. H., 77-7187
 Ruecker, F. A., 77-7142
 Ruhland, D., 77-6710, 77-6711
 Rundell, K., 77-7024, 77-7027
 Rushonik, S. I., 77-6878
 Russell, R. J., 77-7080
 Russo, I. H., 77-7192
 Russo, J., 77-7192
 Ruth, R. F., 77-7089
 Ryabykh, T. P., 77-6731
 Ryan, N., 77-7120
 Rydell, R. E., 77-6834
 Rynbrandt, D., 77-7146
 Rzepka, T., 77-7169
 Sachs, L., 77-7127
 Saffiotti, U., 77-6603
 Sakore, T. D., 77-6851
 Sakula, A., 77-7098
 Sakurai, Y., 77-7040
 Salganicoff, L., 77-6677
 Saliamon, L. S., 77-6823
 Saluja, P. G., 77-6872
 Sams, J., 77-6707
 Sandberg, A. A., 77-7129
 Sanders, C. L., 77-6880
 Sanders, F. K., 77-6639
 Sanford, K. K., 77-7145
 Sano, T., 77-6714
 Santi, L., 77-6850
 Santillana, M., 77-6948
 Sapp, J. P., 77-7101
 Sarin, P. S., 77-7006
 Sarma, D. S., 77-6668
 Sasajima, K., 77-6714
 Saxon, A., 77-7071, 77-7072
 Schaberg, A., 77-6990
 Schaefer-Ridder, M., 77-6699
 Schafer, W., 77-6960
 Schaller, J. P., 77-7082
 Scharp, D., 77-6673
 Scheuer, A., 77-6621
 Schirmmacher, V., 77-7090
 Schlake, W., 77-6710, 77-6711
 Schmahl, D., 77-6609, 77-6767
 Schmatchenko, V. V., 77-7029
 Schmitz, H., 77-6643
 Schneider, A. B., 77-6890, 77-6891
 Schoental, R., 77-6768
 Schor, N. A., 77-6799
 Schottenfeld, D., 77-6633
 Schrumpf, E., 77-7103
 Schulte-Hermann, R., 77-6818
 Schumacher, R. I., 77-6667
 Schumm, D. E., 77-6788
 Schwaab, G., 77-7054
 Schwartz, A. G., 77-6690
 Schwartz, R. S., 77-6945
 Schwarz, K., 77-6613
 Schweizer, J., 77-6743
 Scolnick, E. M., 77-6959
 Scott, D., 77-6937
 Scott, J. S., 77-6886
 Scully, R. E., 77-7157
 Sedliakova, M., 77-6904
 Segerback, D., 77-6824
 Seidegard, J., 77-6753
 Seido, T., 77-6976
 Seki, S., 77-7189
 Seliger, H. H., 77-6720
 Semenova, V. P., 77-6884
 Sen, A., 77-6932
 Sen, N. P., 77-6761
 Senatorova, T. A., 77-6823
 Serafino, X., 77-6908
 Serck-Hanssen, A., 77-7103
 Serebrianyi, A. M., 77-6782
 Sestili, M. A., 77-6615
 Setlow, J. K., 77-6907
 Shafie, S., 77-6865
 Shah, K. V., 77-7008
 Shain, S. A., 77-6877
 Shank, P. R., 77-6941
 Sharma, J. M., 77-7065
 Sharon, N., 77-7068
 Shea, M., 77-7079
 Sheffield, J. B., 77-6943
 Shellenberger, T. E., 77-6867
 Shen, C. K., 77-7025
 Shendrikova, I. A., 77-6733
 Sheridan, J., 77-7030
 Sheveleva, V. S., 77-6653
 Shimaoka, K., 77-6893
 Shimojo, H., 77-6986
 Shimosato, Y., 77-6976
 Shinohara, K., 77-6724
 Shire, J. G., 77-6752
 Shlomei, J., 77-7001
 Shows, T. B., 77-6855
 Shubik, P., 77-6602, 77-6655
 Shubin, A. S., 77-7099
 Shvaidetsky, I. I., 77-6843
 Shvedov, V. L., 77-6884
 Shvydko, N. S., 77-6878
 Sidransky, H., 77-6668
 Siegert, W., 77-6993
 Sigler, A., 77-7077
 Sillett, R. W., 77-6758
 Silverman, D. T., 77-7152
 Simmon, V. F., 77-6798
 Sims, P., 77-6697, 77-6721
 Simsiman, R. C., 77-6747
 Singer, M. F., 77-7014
 Singer, W., 77-7120
 Sinowatz, F., 77-7118
 Sivak, A., 77-6750
 Slaga, T. J., 77-6689, 77-6742, 77-6755
 Sless, F., 77-7080
 Slezarikova, V., 77-6904
 Smirnov, E. A., 77-7095
 Smith, A., 77-7030
 Smith, C. J., 77-6848
 Smith, J. B., 77-7073
 Smith, K. A., 77-7198
 Smith, P. M., 77-6623
 Smith, S. J., 77-6678
 Snoep, M. P., 77-6990
 Sobell, H. M., 77-6851
 Soloviev, V. D., 77-6949
 Solt, D., 77-6658
 Soltani, M., 77-7121
 Soper, C. J., 77-6749
 Sorgente, N., 77-6859
 Sorkin, E., 77-7060
 Souissi, T., 77-7054
 Soukup, S. W., 77-7137
 Spacey, G. D., 77-6783
 Spahr, P. F., 77-6924
 Spanggord, R. J., 77-6798
 Sparkes, R. S., 77-7128
 Speck, W. T., 77-6831
 Spencer, J. L., 77-7089
 Spikes, J. D., 77-6905
 Spitalnik, P. F., 77-6889
 Springer, R. R., 77-6757
 Sproul, E. E., 77-6855
 Sridhar, R., 77-6787
 Stachura, M. E., 77-6890, 77-6891
 Stadaas, J., 77-7103
 Staffeldt, E., 77-6837
 Stanton, M. F., 77-6911
 Stavric, B., 77-6682
 Stegens, N. L., 77-7148
 Stein, Z., 77-6625
 Stephens, E. A., 77-7089
 Stephenson, J. R., 77-7007
 Stern, R. H., 77-7187
 Sternberg, S. S., 77-6863
 Stevenson, M. M., 77-7059
 Stinnett, J. D., 77-7058
 Stoffer, S. S., 77-6887
 Stoltz, D. R., 77-6682, 77-6761
 Strashnenko, S. I., 77-7138
 Straub, K., 77-6725
 Straus, F. H., 77-6889
 Strel'tsova, V. N., 77-6899, 77-7138
 Strober, W., 77-6649, 77-7051
 Strobino, B., 77-6625
 Strong, M. S., 77-7097
 Stroud, A. N., 77-6881
 Styles, J. A., 77-6760
 Subramanian, K. N., 77-7017

- Sugimura, T., 77-6714, 77-6802
 Sullivan, A. K., 77-7079
 Sumithran, E., 77-7158
 Sundaram, A., 77-6804
 Sunderman, F. W., 77-6807
 Surjan, A., 77-6786
 Susser, M., 77-6625
 Suzuki, T., 77-6976
 Swanson, M., 77-7161
 Swartz, M. J., 77-7151
 Swenberg, J. A., 77-6955
 Tabor, E., 77-6989
 Takagi, K., 77-7104
 Takahashi, M., 77-6759
 Takanaka, A., 77-6820
 Takayama, S., 77-6719
 Takeichi, N., 77-7083
 Taketomi, M., 77-6842
 Takita, H., 77-7169
 Tal, J., 77-6919
 Talbott, T. M., 77-7076
 Talcott, R., 77-6830
 Tanaka, Y., 77-7163
 Tarone, R., 77-6756
 Tashian, R. E., 77-7187
 Tatarinova, Iu. I., 77-6949
 Tatosyan, A. G., 77-6975
 Tchipsysheva, T. A., 77-7109
 Tegeris, A., 77-6911
 Tegtmeier, P., 77-7024, 77-7027
 Teich, N. M., 77-6937
 Temin, H. M., 77-6923
 Tenen, D. G., 77-7026
 Terada, M., 77-7179
 Terasaki, P. I., 77-7078
 Tezabwala, B. U., 77-6681
 Themann, H., 77-6710, 77-6711
 Thi, H. L., 77-7079
 Thody, A. J., 77-6872
 Thompson, E. B., 77-7191
 Thomson, A. W., 77-7180
 Thorbecke, G. J., 77-6992
 Till, J. E., 77-7177
 Ting, A., 77-7078
 Ting, C. C., 77-7050
 Todaro, G. J., 77-6932
 Tokes, Z. A., 77-6859
 Tomatis, L., 77-6601, 77-6897
 Tompkins, M., 77-6856
 Toppell, K. L., 77-6757
 Torhorst, J., 77-6685
 Torikata, C., 77-7094
 Toth, B., 77-6854
 Totovic, V., 77-6713
 Toyokawa, H., 77-7163
 Trainin, N., 77-7068
 Tripiet, M. F., 77-6784
 Troll, W., 77-6674, 77-6808
 Trosko, J. E., 77-6746
 Troxler, D. H., 77-6959
 Truelove, J. F., 77-6804
 Truhaut, R., 77-6868, 77-6913
 Trujillo, J. E., 77-6694
 Trump, B. F., 77-6727, 77-7107
 Trumper, P. A., 77-6996
 Ts'o, P. O., 77-6726
 Tsai, C. C., 77-6851
 Tsang, K. Y., 77-6999
 Tscherne, J. S., 77-6789
 Tsuchida, N., 77-6988
 Tsuda, K., 77-7163
 Tsuji, K., 77-6802
 Tsukada, H., 77-6845
 Tsukada, Y., 77-7115
 Tsukagoshi, S., 77-7040
 Tung, A. S., 77-6931
 Turebaev, M. N., 77-6803
 Turner, D. M., 77-6705
 Turner, J. A., 77-6758
 Turusov, V. S., 77-6821
 Tuszyński, G. P., 77-6943
 Tutton, P. J., 77-6857
 Tweedie, D. J., 77-7180
 Uchida, Y., 77-6710, 77-6711
 Ukena, T. E., 77-7182
 Umansky, Iu. A., 77-6680
 Umeda, M., 77-7144
 Umiel, T., 77-7068
 Underhill, C. B., 77-6973
 Urquhart, C., 77-6981
 Utsinger, P. D., 77-7075
 Uwaifo, A. O., 77-6671
 Vaage, J., 77-7034
 Valis, J. D., 77-7008
 van de Pavert, I. V., 77-7125
 Van de Voorde, A., 77-7016
 van den Bergh-Weermah, M., 77-7125
 van der Kogel, A. J., 77-6901
 van Haften, C., 77-7107
 Van Miller, J. P., 77-6814
 Vande Woude, G. F., 77-6969
 Varakis, J. N., 77-6983
 Vardiman, J., 77-6659
 Varet, B., 77-7056
 Varmus, H. E., 77-6919, 77-6941
 77-6942
 Varnes, M. E., 77-6741
 Varshavsky, A. J., 77-7029
 Vasa-Thomas, K. A., 77-7045
 Vasil'eva, N. N., 77-6838
 Vaughan, C. W., 77-7097
 Vaughn, W. K., 77-6873
 Vawter, G., 77-7121
 Velicer, L. F., 77-6936
 Venkatesan, N., 77-7022
 Verney, E., 77-6668
 Vesell, E. S., 77-6678, 77-6756
 Vesely, D. L., 77-6781
 Viaje, A., 77-6742, 77-6755
 Vincent, R. G., 77-7169
 Vogel, C. L., 77-6989
 Vogel, T., 77-7021
 Vogt, P. K., 77-6918
 Volberding, P., 77-6917
 Vorozhtsova, L. N., 77-6878
 Vredevoe, D. L., 77-6963
 Wachmester, C. A., 77-6824
 Wainfan, E., 77-6789
 Wakabayashi, K., 77-6802
 Waldmann, T. A., 77-6649
 Walker, D. L., 77-6983, 77-6984
 Walker, I. G., 77-6787
 Wallcave, L., 77-6854
 Wang, I., 77-7126
 Warburton, D., 77-6625
 Ward, C. M., 77-6894
 Warnaar, S. O., 77-6990
 Warner, N. L., 77-7046
 Warnet, L. M., 77-6913
 Warren, L., 77-6943
 Waszynski, E., 77-6805
 Watanabe, K., 77-6712, 77-6797
 Watanabe, P. G., 77-6826
 Waters, R., 77-6858
 Wattenberg, L. W., 77-6683, 77-6730
 Weatherbee, J. A., 77-6985
 Webb, T., 77-7019, 77-7139
 Webb, T. E., 77-6788
 Weber, M. J., 77-6925
 Wee, V. T., 77-6900
 Wei, E., 77-6830
 Weichselbaum, R., 77-7114
 Weihing, R. R., 77-6985
 Weijer, K., 77-6933
 Weinberger, M. H., 77-7112
 Weinstein, I. B., 77-6835, 77-6971
 Weisburger, J. H., 77-6712, 77-6797
 Weiser, M. M., 77-6980
 Weiss, R., 77-6940
 Weiss, W., 77-6914
 Weissman, S. M., 77-7017
 Wells, P. A., 77-7192
 Welt, S., 77-6992
 Wentzell, B. R., 77-6829
 West, C. E., 77-6676
 West, D., 77-7161
 Westenberger, P., 77-6856
 Westphal, H., 77-6987
 Westwood, J. C., 77-6980
 Weymouth, L. A., 77-6916
 Whur, P., 77-6981
 Wilkinson, P. C., 77-7080
 Willes, R. F., 77-6804
 Williams, D. C., 77-6981
 Williams, D. M., 77-6623
 Williams, G. M., 77-7108
 Williams, R. R., 77-7148
 Williamson, R. C., 77-6864
 Willis, G. W., 77-7106
 Wilson, J., 77-6703
 Wilson, R. B., 77-6734
 Wing, A. L., 77-7154
 Winneker, R. C., 77-6856
 Winocour, E., 77-7020, 77-7021
 Winter, W. G., 77-7100
 Wishnok, J. S., 77-6777
 Witter, R. L., 77-7065, 77-7089
 Woessner, S., 77-7131
 Wolff, D. A., 77-7012
 Wolff, L. H., 77-7082
 Wood, A. W., 77-6699, 77-6722
 Workshop on Lung Cancer, 77-6626
 77-6629, 77-6663
 Wright, T. C., 77-7182
 Wynder, E., 77-7162, 77-7164
 Wynder, E. L., 77-6712
 Yagi, H., 77-6722, 77-6723, 77-6742
 Yahagi, T., 77-6802

Yam, L. T., 77-7134
Yamaguchi, N., 77-6971
Yamamoto, K. R., 77-6941, 77-6942
Yamasaki, E., 77-6702
Yamasaki, H., 77-6835
Yanagihara, K., 77-6976
Yang, J. P., 77-7121
Yang, S. K., 77-6727
Yang, T. J., 77-7117
Yannarell, A., 77-6788
Yano, S., 77-6988
Yatscoff, R. W., 77-6787
Yawata, Y., 77-7185
Yohn, D. S., 77-7082
Yoneyama, T., 77-7100
Yoshida, A., 77-6741

Yoshida, K., 77-6976
Yoshimura, M., 77-6928, 77-6929
Yotti, L. P., 77-6746
Youdim, S., 77-7047
Youn, J. K., 77-6948
Young, H., 77-6959
Yount, W. J., 77-7075
Zacharias, D. E., 77-6698
Zager, E., 77-6735
Zajdela, F., 77-6684
Zaldivar, R., 77-7167
Zanjani, E. D., 77-7064
Zarudin, V. V., 77-7038
Zavada, J., 77-6940
Zedeck, M. S., 77-6862, 77-6863
Zeilig, C. E., 77-7193

Zhdanov, V. M., 77-6638
Zhivetskii, A. V., 77-7166
Zhukova, I. V., 77-7138
Ziegler, J. L., 77-6644
Ziel, H. K., 77-6874
Zil'fian, V. N., 77-6819
Zinkham, W. H., 77-7077
Zorn, S. K., 77-6895
Zuckerman, E. E., 77-6640, 77-6934
zur Hausen, H., 77-6994
ZuRhein, G. M., 77-6983
Zwilling, B. S., 77-7048

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Subject Index

- A-43818**
Mammary Neoplasms, Experimental
Benz(a)anthracene, 7,12-Dimethyl-, 77-6691
- Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-**
Cell Transformation, Neoplastic
Histological Study, Hamster, 77-6793
Mammary Neoplasms, Experimental
Carcinogenic Activity, Mouse, 77-6834
- Acetamide, *N*-(Acetyloxy)-*N*-fluoren-3-yl-**
Mammary Neoplasms, Experimental
Carcinogenic Activity, Mouse, 77-6834
- Acetamide, *N*-(Carbamoylmethyl)-2-diazo-**
Cells, Cultured
Chromatids, 77-6850
DNA Repair, 77-6850
- Acetamide, *N,N*-Dimethyl-**
Erythroleukemia
Cell Differentiation, 77-7179
- Acetamide, *N*-Fluoren-2-yl-**
Acetohydroxamic Acid, *N*-Fluoren-2-yl-
Hydroxylases, 77-6833
Bladder
Glucuronide Metabolite, 77-6836
Metabolism, Rat, 77-6836
Protein, Binding, 77-6836
Cell Transformation, Neoplastic
Animal Model, Review, 77-6601
DNA
Carcinogenic Activity, 77-6835
DNA Replication
Barbituric Acid, 5-Ethyl-5-phenyl-, 77-6837
Liver Neoplasms
Barbituric Acid, 5-Ethyl-5-phenyl-, 77-6837
Carcinoma, 77-6801
p-Cresol, 2,6-Di-*tert*-butyl-, 77-6837
DNA, 77-6801
Fetal Globulins, 77-7109
Histological Study, Rat, 77-7109
Models, Biological, 77-6658
Mammary Neoplasms, Experimental
Carcinogenic Activity, Mouse, 77-6834
Estradiol, 77-6834
Ovariectomy, 77-6834
NADH, NADPH Oxidoreductases
Enzymatic Activity, 77-6799
Salmonella typhimurium
Mutagenic Activity, 77-6802
- Acetamide, *N*-Fluoren-3-yl-**
Mammary Neoplasms, Experimental
Carcinogenic Activity, Mouse, 77-6834
- Acetamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-**
Cells, Cultured
Cell Transformation, Neoplastic, 77-6842
Graft vs Host Reaction
Dose-Response Study, Mouse, 77-7033
Immunity, Cellular
Dose-Response Study, Mouse, 77-7033
Leukemia, Lymphocytic
Antibody Formation, 77-7033
Dose-Response Study, Mouse, 77-7033
- Acetamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)- (cont'd)**
Immunity, Cellular, 77-7033
- Acetamide, Thio-**
Liver Neoplasms
RNA, Messenger, 77-6788
RNA, Messenger
Metabolism, 77-6788
- Acetanilide**
Cytochrome P-450
Metabolism, Liver, 77-6813
- Acetic Acid**
Virus, Rous Sarcoma
Cartilage, 77-6929
- Acetic Acid, (*N*-Acetyl-*N*-(2-phenanthryl)amino) Ester**
DNA
Binding, 77-6815
- Acetic Acid, Bis(*p*-chlorophenyl)-**
Adrenal Gland Diseases
Benz(a)anthracene, 7,12-Dimethyl-, 77-6821
- Acetic Acid, (2,3-Dichloro-4-(2-methylenebutyryl)phenoxy)-**
Barbituric Acid, 5-Ethyl-5-phenyl-
Transferases, 77-6732
Benzo(a)pyrene
Transferases, 77-6732
Cholanthrene, 3-Methyl-
Transferases, 77-6732
- Acetic Acid, Lead Salt**
Diet
Hematopoietic System, 77-6811
Toxicity, Rat, 77-6811
Kidney
Ultrastructural Study, Rat, 77-6811
Kidney Neoplasms
Adenocarcinoma, 77-6805
Adenoma, 77-6805
Species Difference, 77-6805
Sulfanilamide, *N*-2-Thiazolyl-, 77-6805
Liver
Ultrastructural Study, Rat, 77-6811
Sulfanilamide, *N*-2-Thiazolyl-
Co-carcinogenic Activity, 77-6805
- Acetic Acid, Nitrilotri-**
Ozone
Mutagenic Activity, 77-6798
Water Pollutants
Ozone, 77-6798
- Acetic Acid, Phosphono-**
Virus, Herpes Saimiri
Virus Replication, 77-7004
- Acetic Acid, Trifluoro-, Anhydride**
Acetohydroxamic Acid, *N*-Fluoren-2-yl-
Hydroxylases, 77-6833
- Acetic Acid, Vinyl Ester**
Foreign Body Reaction
Ethylene, Chloro- Polymer, 77-6910
Sarcoma
Ethylene, Chloro- Polymer, 77-6910

- Acetohydroxamic Acid, *N*-Fluoren-2-yl-**
 Acetamide, *N*-Fluoren-2-yl-
 Hydroxylases, 77-6833
Acetic Acid, Trifluoro-, Anhydride
 Hydroxylases, 77-6833
Barbituric Acid, 5-Ethyl-5-phenyl-
 Hydroxylases, 77-6833
Bladder
 Metabolism, Rat, 77-6836
 Protein, Binding, 77-6836
Cholanthrene, 3-Methyl-
 Hydroxylases, 77-6833
Hydrochloric Acid
 Hydroxylases, 77-6833
Hydroxylases
 Quantitation Method, 77-6833
Liver Neoplasms
 Models, Biological, 77-6658
Mammary Neoplasms, Experimental
 Carcinogenic Activity, Mouse, 77-6834
Microsomes, Liver
 Quantitation Method, 77-6833
RNA, Ribosomal
 Dose-Response Study, 77-6832
 Hepatectomy, 77-6832
 Liver, Rat, 77-6832
 Poly A, 77-6832
Acetohydroxamic Acid, *N*-Fluoren-3-yl-
 Mammary Neoplasms, Experimental
 Carcinogenic Activity, Mouse, 77-6834
Acetonylacetone
 see 2,5-Hexanedione
Acetophenone, 2-Amino-
 Neoplasms, Experimental
 Animal Model, Guinea Pig, 77-6838
 Neoplasms, Soft Tissue
 Angiosarcoma, 77-6838
 Ovarian Neoplasms
 Leiomyoma, 77-6838
***N*-Acetoxy-*N*-2-acetylaminophenanthrene**
 see Acetic Acid, (*N*-Acetyl-*N*-(2-phenanthryl)amino) Ester
Acetylacetone
 see 2,4-Pentanedione
Acetylcholine
 see Choline Acetate (Ester)
Acid Phosphatase
 Leukemia, Hairy Cell
 Lymphocytes, 77-7132
 Spleen, 77-7134
Acridine, 9-Amino-
 Guanine Nucleotides
 Complex, Crystalline, 77-6851
 DNA, Binding, 77-6851
 Mutagenic Activity, 77-6851
Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-
 Cells, Cultured
 Cell Transformation, Neoplastic, 77-6842
Fibrosarcoma
 Hamster, 77-6842
Salmonella typhimurium
 Mutagenic Activity, 77-6802
Actin
 Mammary Neoplasms, Experimental
 Virus, Murine Mammary Tumor, 77-6943
 Virus, Murine Mammary Tumor
 Isolation and Characterization, 77-6943
 Ultrastructural Study, 77-6943
 Virus Replication, 77-6943
Actinomycin D
 Cell Transformation, Neoplastic
 Cells, Cultured, Review, 77-6608
 Ethane, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)-
 α -Amanitine, 77-6822
 Liver, Rat, 77-6822
 Virus, Polyoma
 RNA Replication, 77-6978
Adamantinoma of Tibia
 see Bone Neoplasms; Tibia
Adenine
 Butyric Acid, 2-Amino-4-(ethylthio)-
 RNA, Transfer, Methyltransferases, 77-6789
Adenoameloblastoma
 see Odontogenic Tumor
Adenocarcinoma
 Colonic Neoplasms
 Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6712
 Histological Study, 77-6712, 77-6856
 Hydrazine, 1,2-Dimethyl-, 77-6856
 Ultrastructural Study, 77-6856
 Hodgkin's Disease
 Case Report, 77-6895
 Hydrazine, 1,2-Dimethyl-
 Cell Cycle Kinetics, 77-7174
 Intestinal Neoplasms
 Hydrazine, 1,2-Dimethyl-, 77-7174
 Kidney Neoplasms
 Acetic Acid, Lead Salt, 77-6805
 Hypertension, 77-7112
 Virus, Herpes Lucke, 77-7194
 Lung Neoplasms
 2-Benzimidazolecarbamic Acid, Methyl Ester
 77-6786
 Epidemiology, 77-7169
 Guanidine, Dodecyl-, Acetate, 77-6786
 Histochemical Study, 77-6736
 Hodgkin's Disease, 77-6895
 Plutonium Oxide, 77-6880
 Ultrastructural Study, 77-6736
 Urea, Ethyl Nitroso-, 77-6897
 Mammary Neoplasms, Experimental
 Benz(a)anthracene, 7,12-Dimethyl-, 77-6702
 Dietary Fats, 77-6676
 Histological Study, 77-6702
 Radiation, Ionizing, 77-6899
 Prostatic Neoplasms
 Androstenedione, 77-6877
 Estrone, 77-6876
 17-Ketosteroids, 77-6877
 Rat, 77-6876
 Testosterone, Propionate, 77-6876
 Rectal Neoplasms
 2-Benzimidazolecarbamic Acid, Methyl Ester
 77-6786
 Guanidine, Dodecyl-, Monoacetate, 77-6786
 Stomach Neoplasms
 Guanidine, 1-Ethyl-3-nitro-1-nitroso-, 77-6710

Adenocarcinoma (cont'd)

- Guanidine, 1-Ethyl-3-nitro-1-nitroso-, 77-6711
- Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6710
- 77-6711

Uterine Neoplasms

- Estradiol, 77-6867
- 4,4'-Stilbenediol, α,α' -Diethyl-, 77-6867

Adenofibroma

- Mammary Neoplasms, Experimental
- Rotenone, 77-6677

Adenoma

- Benz(a)anthracene, 5,6-Dihydro-5,6-dihydroxy-Mouse, 77-6697
- Benz(a)anthracene, 8,9-Dihydro-8,9-dihydroxy-7-methyl-Mouse, 77-6697
- Benz(a)anthracene, 5,6-Dihydro,5,6-epoxy-7-methyl-Mouse, 77-6697
- Benz(a)anthracene, 7-Methyl-Mouse, 77-6697
- Bile Duct Neoplasms
 - Guanidine, Methyl-, 77-6714
 - Nitrous Acid, Sodium Salt, 77-6714
- Colonic Neoplasms
 - Dietary Fats, 77-6797
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6712
 - Histological Study, 77-6712
- Kidney Neoplasms
 - Acetic Acid, Lead Salt, 77-6805
- Liver Neoplasms
 - Case Report, 77-7110
 - Contraceptives, Oral, 77-7110
 - Estradiol, 17-Ethynyl-, 77-7110
 - Histological Study, 77-7110
 - Nitrous Acid, Sodium Salt, 77-6714
- Lung Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-6683
 - Benzo(a)pyrene, 77-6683
 - Carbamic Acid, Ethyl Ester, 77-6878, 77-6879
 - Ethylene, Chloro-, 77-6624
 - Plutonium, 77-6879
 - 4,4'-Stilbenediol, α,α' -Diethyl-, 77-6869
 - Urea, Ethyl Nitroso-, 77-6897
- Parathyroid Neoplasms
 - Case Report, 77-7119
 - Radiation, Ionizing, 77-6885
- Pituitary Neoplasms
 - Prolactin, 77-7120
- Stomach Neoplasms
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6713
- Streptozotocin
 - Liver Neoplasms, 77-6673
- Thyroid Neoplasms
 - Radiation, Ionizing, 77-6635, 77-6889
 - Radioactive Fallout, 77-6882
 - Radiotherapy, 77-6632
- Virus, Kirsten Murine Sarcoma
 - Cell Transformation, Neoplastic, 77-6974

Adenomatosis, Familial Endocrine

- Colonic Neoplasms
- Phenotypic Markers, Review, 77-6652

Adenosine Cyclic 3',5' Monophosphate

- Hepatoma
 - Cells, Cultured, 77-7193
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Epidermis, Mouse, 77-6747

Adenosine Cyclic 3',5' Monophosphate (cont'd)

- Epinephrine, 77-6747
- Isoproterenol, 77-6747

Adenosine, 2'-Deoxy-

- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-Binding, 77-6725

Adenosine Triphosphatase

- Cell Membrane
 - Cell Cycle Kinetics, 77-6750
- Mammary Neoplasms, Experimental
 - Carcinoma, 77-7192
 - Carcinoma, Scirrhus, 77-7192
 - Cell Membrane, 77-7192
 - Ultrastructural Study, Mouse, 77-7192

Adrenal Gland Neoplasms

- Sulfonic Acid, α -Alkene-Dose-Response Study, Rat, 77-6791

Adrenal Glands

- Benz(a)anthracene, 7,12-Dimethyl-Acetic Acid, Bis(*p*-chlorophenyl)-, 77-6821
- Benzophenone, 4,4'-Dichloro-, 77-6821
- Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-77-6821
- Ethanol, 2,2-Bis(*p*-chlorophenyl)-, 77-6821
- Ethylene, 1,1-Bis(*p*-chlorophenyl)-2-chloro-, 77-6821
- Ethylene, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)-77-6821
- Dimethylamine, *N*-Nitroso-Carcinogenic Potential, Rat, 77-6769

Adriamycin

- Cell Transformation, Neoplastic
- Cells, Cultured, Review, 77-6608

Aflatoxin B1

- Cell Transformation, Neoplastic
- Histological Study, Hamster, 77-6793
- Cells, Cultured
 - DNA Replication, 77-6667
- DNA
 - Binding, 77-6614
- Intestines
 - Tissue Distribution, 77-6669
- LD 50
 - Age Factors, Mouse, 77-6672
- Liver
 - Metabolism, 77-6670
 - Metabolism, Mink, 77-6669
 - Proteins, 77-6668
 - Ribosomes, 77-6668
 - Tissue Distribution, 77-6669
- Liver Neoplasms
 - Carcinoma, 77-6801
 - DNA, 77-6801
 - Models, Biological, 77-6658
- Metabolism
 - Cow, 77-6670
- Rubratoxin B
 - Body Weight, 77-6672
 - LD 50, 77-6672
- Ultraviolet Rays
 - DNA Repair, 77-6667
 - DNA Replication, 77-6667

Agammaglobulinemia

- Infectious Mononucleosis

- Agammaglobulinemia (cont'd)**
 Immunodeficiency, 77-7121
 Lymphocytes
 Erythropoiesis, 77-7064
 Immunoglobulins, 77-7064
 B-Lymphocytes
 Immunosuppression, 77-7064
 T-Lymphocytes
 Immunosuppression, 77-7064
 Thymoma
 Lymphocytes, 77-7064
 Virus, Epstein-Barr
 Immunodeficiency, 77-7121
 Virus, Measles
 Immunodeficiency, 77-7121
- Aging**
 Benz(a)anthracene, 7,12-Dimethyl-
 Species Difference, 77-6690
 Epinephrine
 Neural Transmission, Review, 77-6653
 Neurilemmoma
 Radiation, Ionizing, 77-6901
 Norepinephrine
 Neural Transmission, Review, 77-6653
- Agrobacterium tumefaciens***
 Plant Tumors
 Metabolism, 77-7186
- Air Pollutants**
 Aroclor 1254
 Mutagenic Activity, 77-6830
 Benzo(a)pyrene
 Mutagenic Activity, 77-6830
 7,8-Benzoflavone
 Mutagenic Activity, 77-6830
 Polycyclic Hydrocarbons
 Mutagenic Activity, 77-6830
- Air Pollution**
 Lung Neoplasms
 Epidemiology, USSR, 77-6664
- Alanine Aminotransferase**
 Cadmium Sulfate
 Enzymatic Activity, 77-6812
 Nitrous Acid, Sodium Salt
 Vitamin E, 77-6717
- Alanine, 3-(3,4-Dihydroxyphenyl)-**
 Breast Neoplasms
 Neoplasm Metastasis, 77-6619
 Mammary Neoplasms, Experimental
 Neoplasm Metastasis, 77-6619
 Prolactin, 77-6619
- Alkaline Phosphatase**
 Cadmium Sulfate
 Enzymatic Activity, 77-6812
 Carbon Tetrachloride
 Enzymatic Activity, 77-6823
- Alkylating Agents**
 Immunosuppression
 Carcinogenic Activity, Review, 77-6609
- Alpha Particles**
 Lung Neoplasms
 Epidemiology, Review, 77-6630
 Lymphoma
 Epidemiology, Review, 77-6630
- Alpha Particles (cont'd)**
 Occupational Hazard
 Epidemiology, Review, 77-6630
 Sarcoma, Osteogenic
 Epidemiology, Review, 77-6630
- α -Amanitine**
 Ethane, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)-
 Actinomycin D, 77-6822
 Virus, Polyoma
 RNA Replication, 77-6978
- Amino Acids**
 Hepatoma
 Diethylamine, *N*-Nitroso-, 77-6765
 Nickel Sulfide
 Dissolution Kinetics, 77-6807
- o*-Aminodiphenyl**
 see 2-Biphenylamine
- Aminopterin**
 Virus, Epstein-Barr
 Antigens, Viral, 77-6994
- Aminotransferases**
 Isoenzymes
 Cell Differentiation, 77-7015
 Cell Transformation, Neoplastic, 77-7015
 Lung Neoplasms
 Isolation and Characterization, 77-7195
 Virus, Polyoma
 Cell Transformation, Neoplastic, 77-7015
 Virus, Rous Sarcoma
 Cell Transformation, Neoplastic, 77-7015
- Anabesine**
 Nicotine, 1'-Nitroso-1'-demethyl-
 Nitrosation Kinetics, 77-6707
- Anabesine, 1-Nitroso-**
 Respiratory System
 Carcinogenic Potential, Hamster, 77-6706
- Androgens**
 Hepatoma
 Epidemiology, Review, 77-6621
 Liver Neoplasms
 Hyperplasia, 77-6621
 Neoplasms, Multiple Primary
 Receptors, Hormone, Review, 77-6617
 Ultrastructural Study
 Prostate, 77-7118
- 5 α -Androstan-3-one, 17 β -Hydroxy-**
 Prostate
 Ultrastructural Study, 77-7118
- 5 α -Androstane-3 α ,17 α -diol**
 Prostate
 Ultrastructural Study, 77-7118
- Androstenedione**
 Prostatic Neoplasms
 Adenocarcinoma, 77-6877
- Angioma**
 see Hemangioma
- Angiosarcoma**
 Arsenic
 Epidemiology, Review, 77-6623
 Ethylene, Chloro-
 Epidemiology, Review, 77-6623

Angiosarcoma (cont'd)

- Head and Neck Neoplasms
 - Case Report, 77-6894
 - Radiation, Ionizing, 77-6894
- Hemangioma
 - Radiation, Ionizing, 77-6894
- Liver Neoplasms
 - Ethylene, Chloro-, 77-6624, 77-6825
 - Occupational Hazard, 77-6622
- Neoplasms, Soft Tissue
 - Acetophenone, 2-Amino-, 77-6838
- Nitrous Acid, Sodium Salt
 - Guanidine, Methyl-, 77-6714
- Peritoneal Neoplasms
 - Indole-3-acrylic Acid, 77-6838

Aniline

- Oxygen
 - Sludge, 77-6852

Aniline, *N,N*-Dimethyl-

- Oxygen
 - Sludge, 77-6852

Aniline, *N,N*-Dimethyl-*p*-phenylazo-

- Hepatoma
 - Immune Response, 77-6847
- Salmonella typhimurium*
 - Mutagenic Activity, 77-6802

Aniline, *N*-Methyl-*N*-nitroso-

- Cells, Cultured
 - Mutagenic Activity, 77-6770

Aniline, 2,4,6-Trimethyl-

- Hepatoma
 - Chromosome Abnormalities, 77-6849
- Pituitary Neoplasms
 - Chromosome Abnormalities, 77-6849
 - Karyotyping, 77-6849

-Anthracenamide

- Salmonella typhimurium*
 - Mutagenic Activity, 77-6795

Antibodies

- Nasopharyngeal Neoplasms
 - Lymphocyte Cytotoxicity, 77-7054
- Sarcoma, Osteogenic
 - Immune Serums, 77-7031
- Virus, Rauscher Murine Leukemia
 - Isolation and Characterization, 77-7056

Antibodies, Neoplasm

- Sarcoma, Mast Cell
 - Ascitic Fluid, 77-7049
 - Chromium Release Assay, 77-7049

Antibodies, Viral

- Ataxia Telangiectasia
 - Virus, Epstein-Barr, 77-6991
- Burkitt's Lymphoma
 - Virus, Epstein-Barr, 77-7055
- Virus, Epstein-Barr
 - Methanol, 77-7055
- Virus, Herpes Simplex 1
 - Immunity, Cellular, 77-7052, 77-7053

Antibody Formation

- Benzo(a)pyrene
 - Antigens, Heterogenetic, 77-7048
 - IgG, 77-7048

Antibody Formation (cont'd)

- IgM, 77-7048
- Benzo(e)pyrene
 - Antigens, Heterogenetic, 77-7048
- Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 - Dose-Response Study, Mouse, 77-7033
- Leukemia, Lymphocytic
 - Acetamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 - 77-7033
- T-Lymphocytes
 - Helper Activity, 77-7067
 - Immunosuppression, 77-7067
- Neoplasms, Experimental
 - Transplantation, Homologous, 77-7030
- Virus, Gross Murine Leukemia
 - Viral Vaccines, 77-7043
- Virus, Murine Leukemia
 - Viral Vaccines, 77-7043

Antibody Specificity

- Virus, Baboon
 - Virus, RD-114, 77-7006
- Virus, Friend Murine Leukemia
 - Glycoproteins, 77-6960
- Virus, Gross Murine Leukemia
 - Virus, Friend Murine Leukemia, 77-7043
- Virus, Murine Leukemia
 - Immune Serums, 77-7043

Antigen-Antibody Reactions

- Ataxia Telangiectasia
 - Virus, Epstein-Barr, 77-6991
- Burkitt's Lymphoma
 - Virus, Epstein-Barr, 77-7055
- Hepatoma
 - Virus, Hepatitis, 77-6989
- Hodgkin's Disease
 - Virus, Epstein-Barr, 77-6994
- Leukemia, Lymphocytic
 - Virus, Epstein-Barr, 77-6994
- Lymphoma
 - Virus, Epstein-Barr, 77-6994
- Nasopharyngeal Neoplasms
 - Virus, Epstein-Barr, 77-6994, 77-7054
- Sarcoma, Reticulum Cell
 - Virus, Epstein-Barr, 77-6994
- α -Toluidine, 4-(α -Tolylazo)-
 - Benzoic Acid, 2-Amino-3-hydroxy-, 77-6843
 - Cell Transformation, Neoplastic, 77-6843
- Virus, B77
 - Virus, Murine Leukemia, 77-6972
- Virus, C-Type RNA Tumor
 - Virus, Moloney Murine Leukemia, 77-6966
- Virus, Epstein-Barr
 - Lymphotoxin, 77-7054
- Virus, Feline Leukemia
 - Antigens, Viral, 77-7082
- Virus, Friend Murine Leukemia
 - Glycoproteins, 77-6960
 - Virus, Feline Leukemia, 77-6960
- Virus, Gross Murine Leukemia
 - Immune Serums, 77-7043
- Virus, Il'in-Bykovskii
 - Virus, Mason-Pfizer Monkey, 77-7005
- Virus, Kirsten Murine Sarcoma
 - Isolation and Characterization, 77-6972
- Virus, Moloney Murine Leukemia
 - Antigens, Neoplasm, 77-7085

Antigen-Antibody Reactions (cont'd)

- Virus, Murine Leukemia
- Immune Serums, 77-7043

Antigenic Determinants

- Carcinoma, Epidermoid
- Cholanthrene, 3-Methyl-, 77-7083
- Graft Rejection, 77-7083
- Plasmacytoma
- Histocompatibility Antigens, 77-7046
- Virus, Avian Leukosis-Sarcoma
- Glycoproteins, 77-6919
- Virus, B77
- Cell Transformation, Neoplastic, 77-6972
- Virus, Il'in-Bykovskii
- Virus, Mason-Pfizer Monkey, 77-7005
- Virus, Moloney Murine Sarcoma
- Virus, Feline Leukemia, 77-6969
- Virus, Murine Leukemia
- Mouse, AKR/New Zealand, 77-6961
- Viral Proteins, 77-6964
- Virus Replication, 77-6964

Antigens

- Leukemia, Lymphoblastic
- B-Lymphocytes, 77-7074
- T-Lymphocytes, 77-7074
- Leukemia, Lymphocytic
- B-Lymphocytes, 77-7079
- Leukemia, Myeloblastic
- B-Lymphocytes, 77-7074
- T-Lymphocytes, 77-7074
- B-Lymphocytes
- Isolation and Characterization, 77-7079
- Lymphoma
- Immune Response, Hamster, 77-7045
- Sarcoma
- Cholanthrene, 3-Methyl-, 77-7086
- Sarcoma, Osteogenic
- Immune Serums, 77-7031
- α -Toluidine, 4-(α -Tolylazo)-
- Binding, Liver, 77-6843

Antigens, Heterogenetic

- Benzo(a)pyrene
- Antibody Formation, 77-7048
- Benzo(e)pyrene
- Antibody Formation, 77-7048

Antigens, Neoplasm

- Lymphoma
- Virus, Moloney Murine Leukemia, 77-7085
- Mammary Neoplasms, Experimental
- Immunity, Active, 77-7041
- Neoplasms
- Immune Response, 77-6647
- Ovarian Neoplasms
- Immunity, Active, 77-7041
- Plasmacytoma
- Immune Response, 77-7046
- Sarcoma, Mast Cell
- Growth, 77-7049
- Immunity, Cellular, 77-7049
- Virus, Moloney Murine Leukemia
- Antigen-Antibody Reactions, 77-7085
- Lymphocyte Cytotoxicity, 77-7085
- Migration Inhibitory Factor, 77-7085
- Virus, Polyoma
- Cell Membrane, 77-6979

Antigens, Neoplasm (cont'd)

- Temperature Sensitive Mutants, 77-6979
- Virus, SV40
- Cell Transformation, Neoplastic, 77-7070
- Histocompatibility Antigens, 77-7084

Antigens, Viral

- Burkitt's Lymphoma
- Virus, Epstein-Barr, 77-6998, 77-6999
- Fibrosarcoma
- Virus, Polyoma, 77-7091
- Leukemia, Radiation-Induced
- Virus, Murine Leukemia, 77-6962
- Leukoencephalopathy, Progressive Multifocal
- Virus, Polyoma, JC, 77-6984
- Lymphocytes
- Virus, Bovine Leukemia, 77-6938
- Lymphoma
- Virus, Epstein-Barr, 77-6994
- Lymphosarcoma
- Virus, Bovine Leukemia, 77-6938
- Mammary Neoplasms, Experimental
- Virus, Feline Leukemia, 77-6933
- Virus, RD-114, 77-6933
- Neoplasms, Experimental
- Virus, Murine Leukemia, 77-7090
- Virus, C-Type RNA Tumor
- Cell Transformation, Neoplastic, 77-6966
- Immune Serums, 77-6966
- Virus Replication, 77-6966
- Virus, D-Type RNA Tumor
- Virus, Il'in-Bykovskii, 77-7005
- Virus, Epstein-Barr
- Aminopterin, 77-6994
- Cell Membrane, 77-6995
- Complement Fixation, 77-6993
- DNA, Binding, 77-6993
- Hypoxanthine, 77-6994
- Radioimmunoassay, 77-6995
- Ultrastructural Study, 77-6996
- Uridine, 2'-Deoxy-5-iodo-, 77-6994
- Virus, Feline Leukemia
- Antigen-Antibody Reactions, 77-7082
- Cell Membrane, 77-7082
- Cell Transformation, Neoplastic, 77-6934
- Cells, Cultured, 77-6935, 77-6957
- Solubilization, 77-7082
- Virus, Feline Sarcoma
- Cell Transformation, Neoplastic, 77-6934
- Virus, Friend Murine Leukemia
- Cells, Cultured, 77-6957, 77-6958
- Virus, Gibbon Ape Lymphoma
- Cells, Cultured, 77-6957
- Virus, Gross Murine Leukemia
- Cells, Cultured, 77-6957
- Viral Proteins, 77-6947
- Virus, Moloney Murine Leukemia
- Cells, Cultured, 77-6957
- Virus, Murine Mammary Tumor
- Hepatoma, 77-6942
- Immune Response, 77-7081
- Lymphocytes, 77-7081
- Virus, Vesicular Stomatitis, 77-6940
- Virus, Polyoma
- Embryo, Hamster, 77-7091
- Isolation and Characterization, 77-7091
- Virus, Rauscher Murine Leukemia
- Cells, Cultured, 77-6957

- Antigens, Viral (cont'd)**
 Virus, SV40
 DNA, Binding, 77-7026
 Hybrid Cells, 77-7011
 Temperature Sensitive Mutants, 77-7026
- Antilymphocyte Serum**
 Sarcoma
 Ethylene, Chloro- Polymer, 77-7035
- Antimetabolites, Antineoplastic**
 Immunosuppression
 Carcinogenic Activity, Review, 77-6609
- Antineoplastic Agents**
 Immunosuppression
 Carcinogenic Activity, Review, 77-6609
- Antipain**
 DNA Repair
 Escherichia coli, 77-6674
- Antipyrone, 4-(Dimethylamino)-**
 Cytochrome P-450
 Metabolism, Liver, 77-6813
 Nitrous Acid, Sodium Salt
 γ -Tocopherol, 77-6717
 α -Tocopherolquinone, 77-6717
 Vitamin E, 77-6717
- Aprotinin**
 see Kallikrein-Trypsin Inactivator
- Aroclor 1254**
 Air Pollutants
 Mutagenic Activity, 77-6830
 Polycyclic Hydrocarbons
 Mutagenic Activity, 77-6830
- Arsanilic Acid**
 Diet
 Hematopoietic System, 77-6811
 Toxicity, Rat, 77-6811
 Kidney
 Ultrastructural Study, Rat, 77-6811
 Liver
 Ultrastructural Study, Rat, 77-6811
- Arsenic**
 Angiosarcoma
 Epidemiology, Review, 77-6623
 Liver Neoplasms
 Occupational Hazard, 77-6622
 Occupational Hazard
 Review, 77-7171
- Arsenic Acid, Sodium Salt**
 Dosage Forms
 Excretion, Rat, 77-6809
 Tissue Distribution, Rat, 77-6809
 Selenium
 Excretion, Rat, 77-6809
 Tissue Distribution, Rat, 77-6809
- Arsenious Acid, Sodium Salt**
 Cells, Cultured
 Cell Survival, 77-6810
Escherichia coli
 DNA Repair, 77-6808
 Galactosidases, 77-6808
 RNA Replication, 77-6808
 Selenious Acid, Disodium Salt
 Cell Survival, 77-6810
- Arsenious Acid, Sodium Salt (cont'd)**
 Ultraviolet Rays
 DNA Repair, 77-6808
- Aryl Hydrocarbon Hydroxylases**
 Benz(a)anthracene
 Genetics, 77-6756
 Benz(a)anthracene, 7,12-Dimethyl-
 Benzo(b)triphenylene, 77-6689
 Skin, Mouse, 77-6689
 Benzo(a)pyrene
 Metabolism, 77-6720, 77-6740
 Benzo(b)triphenylene
 Epidermis, Mouse, 77-6755
 Skin, Mouse, 77-6689
 7,8-Benzoflavone
 DNA, Binding, 77-6755
 Epidermis, Mouse, 77-6755
 Carbon Monoxide
 Enzymatic Activity, 77-6705
 Cholanthrene, 3-Methyl-
 Dexamethasone, 77-6755
 Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-, 77-6754
 Enzymatic Activity, 77-6752
 Indole-3-acetic Acid, 1-(*p*-Chlorobenzoyl)-5-
 methoxy-2-methyl-, 77-6755
 Liver, Mouse, 77-6754
 Liver, Rat, 77-6751
 3,5-Pyrazolidinedione, 4-Butyl-1-(*p*-hydroxyphenyl)-
 2-phenyl-, 77-6755
 Seclazone, 77-6755
 Strain Difference, Mouse, 77-6754
 Genetics
 Models, Theoretical, 77-6752
 Monocytes, 77-6756
 Mouse, 77-6752
 Hydro-Lyases
 Liver, Rat, 77-6751
 Lung Neoplasms
 Lymphocytes, 77-6757
 Macrophages, 77-6757
 Smoking, 77-6757
 Phenanthrene, 9,10-Dihydro-9,10-epoxy-
 Liver, Rat, 77-6751
 Smoking
 Lymphocytes, 77-6757
 Macrophages, 77-6757
- Asbestos**
 Carcinoma, Bronchogenic
 Epidemiology, Review, 77-6627
 Colonic Neoplasms
 Epidemiology, 77-6914
 Enzymatic Activity, 77-6912
 Lung, 77-6912
 Galactosidases, 77-6912
 Glucosaminidase, 77-6912
 Glucuronidase, 77-6912
 Lung Neoplasms
 Epidemiology, 77-6914, 77-7173
 Epidemiology, Review, 77-6627
 Mesothelioma
 Epidemiology, Review, 77-6627
 Occupational Hazard
 Epidemiology, Review, 77-6628
 Particle Size
 Carcinogenic Activity, Review, 77-6628
 Phagocytosis, 77-6912

- Asbestos (cont'd)**
 Pleural Neoplasms
 Epidemiology, Review, 77-6627
 Smoking
 Co-carcinogenic Activity, Review, 77-6627
 Co-carcinogenic Effect, 77-7173
 Epidemiology, 77-7173
 Epidemiology, Review, 77-6628
 Stomach Neoplasms
 Epidemiology, 77-6914
 Toxicology
 Rabbit, 77-6913
- Ascorbic Acid**
 Neoplasms, Experimental
 Cholanthrene, 3-Methyl-, 77-6679
 Dose-Response Study, 77-6679
 Growth, 77-6679
 Nitrous Acid, Sodium Salt
 Gastric Juice, 77-6717
- Aspartate Aminotransferase**
 Cadmium Sulfate
 Enzymatic Activity, 77-6812
- Aspergillus flavus***
 Mycotoxins
 Isolation and Characterization, 77-6671
- Astrocytoma**
 IgM
 Transplantation Immunology, 77-7036
 Lymphocytes
 Transplantation Immunology, 77-7036
 Nervous System Neoplasms
 Urea, 1-Butyl-1-nitroso-, 77-6778
- Ataxia Telangiectasia**
 Chromosome Aberrations
 Cells, Cultured, 77-7019
 Virus, Epstein-Barr
 Antibodies, Viral, 77-6991
 Antigen-Antibody Reactions, 77-6991
 Genetics, 77-6991
 Immune Response, 77-6991
 Virus, SV40
 Cell Transformation, Neoplastic, 77-7019
 Chromosomes, 77-7139
- Autoimmune Diseases**
 Immune Response
 Review, 77-6649
- Azathioprine**
 Sarcoma
 Ethylene, Chloro- Polymer, 77-7035
- 1H-Azepine, Hexahydro-1-nitroso-**
 1,6-Hexanediol
 Metabolism, Liver, 77-6764
 Maternal-Fetal Exchange
 Hamster, 77-6759
 Nucleic Acids
 1,6-Hexanediol, 77-6764
- 2-Azetidinecarboxylic Acid**
 Virus, Feline Leukemia
 Viral Proteins, 77-6936
- Bacteroides fragilis***
 Fluoren-2-amine
 Carcinogenic Metabolite, 77-6831
- Barbituric Acid, 5-Ethyl-5-phenyl-**
 Acetic Acid, (2,3-Dichloro-4-(2-methylenebutyryl)phenoxy)-
 Transferases, 77-6732
 Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 Hydroxylases, 77-6833
 Benzene, 1-Chloro-2,4-dinitro-
 Transferases, 77-6732
 Benzene, 1-(Chloromethyl)-4-nitro-
 Transferases, 77-6732
 Butyric Acid, 2-Amino-4-(ethylthio)-
 RNA, Transfer, Methyltransferases, 77-6789
 Dimethylamine, *N*-Nitroso-
 Mutagenic Activity, 77-6770
 DNA Replication
 Acetamide, *N*-Fluoren-2-yl-, 77-6837
 Epoxide Hydratases
 Enzymatic Activity, 77-6753
 Hepatoma
 Hydroxylases, Estrogen, 77-7200
 Liver Neoplasms
 Acetamide, *N*-Fluoren-2-yl-, 77-6837
 Orotic Acid
 Microsomes, Liver, 77-6678
 RNA, Ribosomal
 Liver, Rat, 77-6678
 Transferases
 Intestine, Rat, 77-6732
- Benz(a)anthracene**
 Aryl Hydrocarbon Hydroxylases
 Genetics, 77-6756
 Biogenic Amines
 Rat, 77-6687
 Carcinogenic Metabolite
 Mouse, 77-6699
 Mutagenic Activity, 77-6721
 Cells, Cultured
 Mutagenic Activity, 77-6721
 Neoplasms, Experimental
 Carcinogenic Metabolite, 77-6699
Salmonella typhimurium
 Mutagenic Activity, 77-6721
- Benz(a)anthracene, 5,6-Dihydro-5,6-dihydroxy-**
 Adenoma
 Mouse, 77-6697
 Lung
 Metabolism, 77-6697
- Benz(a)anthracene, 8,9-Dihydro-8,9-dihydroxy-7-methyl-**
 Adenoma
 Mouse, 77-6697
 Lung
 Metabolism, 77-6697
- Benz(a)anthracene, 5,6-Dihydro,5,6-epoxy-7-methyl-**
 Adenoma
 Mouse, 77-6697
 Carcinoma
 Mouse, 77-6697
 Lung
 Metabolism, 77-6697
- Benz(a)anthracene, 7,12-Dimethyl-**
 Adrenal Gland Diseases
 Acetic Acid, Bis(*p*-chlorophenyl)-, 77-6821
 Benzophenone, 4,4'-Dichloro-, 77-6821
 Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-
 77-6821

Benz(a)anthracene, 7,12-Dimethyl- (cont'd)
 Ethanol, 2,2-Bis(*p*-chlorophenyl)-, 77-6821
 Ethylene, 1,1-Bis(*p*-chlorophenyl)-2-chloro-, 77-6821
 Ethylene, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)-
 77-6821

Aging
 Species Difference, 77-6690
Aryl Hydrocarbon Hydroxylases
 Skin, Mouse, 77-6689
Benzo(a)pyrene
 Metabolism, Mouse, 77-6733
Benzo(b)triphenylene
 Aryl Hydrocarbon Hydroxylases, 77-6689

Biogenic Amines
 Rat, 77-6687
1,3-Butadiene, 2-Chloro-
 Carcinogenic Activity, 77-6819
Carcinogenic Metabolite
 Isolation and Characterization, 77-6698

Cell Differentiation
 Cells, Cultured, 77-6686
Cell Transformation, Neoplastic
 Strain Difference, Mouse, 77-7144
Cells Cultured

Cell Transformation, Neoplastic, 77-6686
Contact Inhibition
 Cell Transformation, Neoplastic, 77-7144

DNA, Binding
 Species Difference, 77-6690

Fibroblasts
 DNA, Binding, 77-6690

LH
 Plasma Levels, 77-6695

Lung Neoplasms
 Adenoma, 77-6683

Mammary Neoplasms, Experimental
 A-43818, 77-6691
 Adenocarcinoma, 77-6702
 Benzene, Isocyanato-, 77-6683
 Benzene, (2-Isothiocyanatoethyl)-, 77-6683
 Benzene, (2-Isothiocyanatomethyl)-, 77-6683
 Diet, 77-7162
 Estradiol, Ethinyl-11 α -methoxy-, 77-6695, 77-6696
 LH-FSH Releasing Hormone, 77-6691
 Prolactin, 77-6619, 77-6693, 77-6694
 Prolactin Release Inhibiting Hormone, 77-6691
 Thiocyanic Acid, Phenylmethyl Ester, 77-6683

Mouth Neoplasms
 Hamster, 77-6794

NADH, NADPH Oxidoreductases
 Enzymatic Activity, 77-6799

Prolactin
 Progesterone, 77-6695

Receptors, Hormone
 Mammary Neoplasms, Experimental, 77-6692

Retinol, Hexadecanoate
 Ultrastructural Study, Epidermis, Mouse, 77-6688

Salmonella typhimurium
 Mutagenic Activity, 77-6795

Skin Neoplasms
 Benzo(b)triphenylene, 77-6689
 Papilloma, 77-6685
 Precancerous Conditions, 77-6688
 Retinol, Hexadecanoate, 77-6688
 Ro 10-9359, 77-6685

Submandibular Gland
 Cell Transformation, Neoplastic, 77-6686

Benz(a)anthracene, 7,12-Dimethyl- (cont'd)
 12-*O*-Tetradecanoylphorbol-13-acetate
 Hair, Mouse Tail, 77-6743

Benz(a)anthracene, 7-Methyl-
Adenoma
 Mouse, 77-6697
Lung
 Metabolism, 77-6697
 Mouse, 77-6697

Benz(c)acridine
Methylation
 Carcinogenic Activity, 77-6684

Benz(e)acephenanthrylene
Smoking
 Carcinogen, Chemical, 77-6626

Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
 2,3-Butanediol, 1,4-Dimercapto-
 Mitochondria, Liver, 77-6846
 Oxidative Phosphorylation, 77-6846
 2,3-Butanedione
 Mitochondria, Liver, 77-6846
 Oxidative Phosphorylation, 77-6846
Cholangioma
Besnoitia jellisoni, 77-7061
Toxoplasma gondii, 77-7061
Hepatoma
Besnoitia jellisoni, 77-7061
Toxoplasma gondii, 77-7061
 2,5-Hexanedione
 Mitochondria, Liver, 77-6846
 Oxidative Phosphorylation, 77-6846
Liver Neoplasms
 Catalase, 77-6845
 Fetal Globulins, 77-6848, 77-7109
 Histological Study, 77-6845
 Histological Study, Rat, 77-7109
 Models, Biological, 77-6658
 Rat, 77-6848
 Ultrastructural Study, 77-6845
 2,4-Pentanedione
 Mitochondria, Liver, 77-6846
 Oxidative Phosphorylation, 77-6846

Benzene
 1,3-Butadiene, 2-Chloro-
 Carcinogenic Activity, 77-6819

Benzene, 1-Chloro-2,4-dinitro-
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Transferases, 77-6732
Benzo(a)pyrene
 Transferases, 77-6732
Cholanthrene, 3-Methyl-
 Transferases, 77-6732

- Benzene, 1-(Chloromethyl)-4-nitro-**
Barbituric Acid, 5-Ethyl-5-phenyl-
Transferases, 77-6732
Benzo(a)pyrene
Transferases, 77-6732
Cholanthrene, 3-Methyl-
Transferases, 77-6732
- Benzene, (Epoxyethyl)-**
Epoxide Hydratases
Enzymatic Activity, 77-6753
- Benzene, Isocyanato-**
Mammary Neoplasms, Experimental
Benz(a)anthracene, 7,12-Dimethyl-, 77-6683
- Benzene, (2-Isothiocyantoethyl)-**
Lung Neoplasms
Benzo(a)pyrene, 77-6683
Mammary Neoplasms, Experimental, 77-6683
Mammary Neoplasms, Experimental
Benz(a)anthracene, 7,12-Dimethyl-, 77-6683
Stomach Neoplasms
Benzo(a)pyrene, 77-6683
Mammary Neoplasms, Experimental, 77-6683
- Benzene, (2-Isothiocyantomethyl)-**
Lung Neoplasms
Benzo(a)pyrene, 77-6683
Mammary Neoplasms, Experimental, 77-6683
Mammary Neoplasms, Experimental
Benz(a)anthracene, 7,12-Dimethyl-, 77-6683
Stomach Neoplasms
Benzo(a)pyrene, 77-6683
Mammary Neoplasms, Experimental, 77-6683
- Benzidine**
Bladder Neoplasms
Blood Proteins, 77-6853
Occupational Hazard, 77-6853
Blood Proteins
Immune Response, 77-6853
Environmental Hazard
Food-Chain Transfer, 77-6796
Oxygen
Sludge, 77-6852
Piperonyl Butoxide
Metabolism, Aquatic Organisms, 77-6796
Soil
Degradation, 77-6796
- Benzidine, 3,3'-Dimethyl-**
Oxygen
Sludge, 77-6852
- Benzidine, Tetramethyl-**
Oxygen
Sludge, 77-6852
- 2-Benzimidazolecarbamic Acid, Methyl Ester**
Lung Neoplasms
Adenocarcinoma, 77-6786
Transplacental Carcinogenesis, 77-6786
Lymphoma
Transplacental Carcinogenesis, 77-6786
Lymphosarcoma
Transplacental Carcinogenesis, 77-6786
Methane, Dichloro-
Nitroso Compounds, 77-6786
- 2-Benzimidazolecarbamic Acid, Methyl Ester (cont'd)**
Nitroso Compounds
Isolation and Characterization, 77-6786
Rectal Neoplasms
Adenocarcinoma, 77-6786
Transplacental Carcinogenesis, 77-6786
- 1,2-Benzisothiazolin-3-one, 1,1-Dioxide**
Fetal Death
Mutagenic Activity, 77-6681
Germ Cells
Mutagenic Activity, 77-6681
- 1,2-Benzisothiazolin-3-one, 1,1-Dioxide, Sodium Salt**
Salmonella typhimurium
Mutagenic Activity, 77-6682
- Benzo(a)pyren-1-ol**
Phenol, (1,1-Dimethylethyl)-4-methoxy-
Metabolism, Liver, Mouse, 77-6730
- Benzo(a)pyren-2-ol**
Hyperplasia
Epidermis, Mouse, 77-6722
- Benzo(a)pyren-3-ol**
Benzo(a)pyrene
Phenol, (1,1-Dimethylethyl)-4-methoxy-, 77-6730
7,8-Benzoflavone
Cell Survival, 77-6731
Cells, Cultured
Cell Survival, 77-6731
Metabolism, 77-6729
Fibroblasts
Cell Survival, 77-6731
L Cells
Cell Survival, 77-6731
Phenol, (1,1-Dimethylethyl)-4-methoxy-
Metabolism, Liver, Mouse, 77-6730
- Benzo(a)pyren-6-ol**
7,8-Benzoflavone
Cell Survival, 77-6731
Cells, Cultured
Cell Survival, 77-6731
Fibroblasts
Cell Survival, 77-6731
L Cells
Cell Survival, 77-6731
- Benzo(a)pyren-9-ol**
Cells, Cultured
Metabolism, 77-6729
Hyperplasia
Epidermis, Mouse, 77-6722
- Benzo(a)pyrene**
Acetic Acid, (2,3-Dichloro-4-(2-methylenebutyryl)phenoxy)-
Transferases, 77-6732
Air Pollutants
Mutagenic Activity, 77-6830
Antibody Formation
IgG, 77-7048
IgM, 77-7048
Antigens, Heterogenetic
Antibody Formation, 77-7048
Aryl Hydrocarbon Hydroxylases
Metabolism, 77-6720, 77-6740
Benz(a)anthracene, 7,12-Dimethyl-
Metabolism, Mouse, 77-6733
Benzene, 1-Chloro-2,4-dinitro-

Benzo(a)pyrene (cont'd)

- Transferases, 77-6732
- Benzene, 1-(Chloromethyl)-4-nitro-
Transferases, 77-6732
- Benzo(a)pyren-3-ol
Phenol, (1,1-Dimethylethyl)-4-methoxy-, 77-6730
- Bronchi
Metabolism, 77-6727
Organ Culture, 77-6727
- Carcinogenic Metabolite
Mutagenic Activity, 77-6721
- Cell Transformation, Neoplastic
Histological Study, Hamster, 77-6793
- Cells, Cultured
Histological Study, 77-6734
Metabolism, 77-6729
Metabolism, Embryo, 77-6739
Mutagenic Activity, 77-6721
- Cholanthrene, 3-Methyl-
Metabolism, Pancreas, 77-6741
- Cytochrome P-450
Metabolism, Liver, 77-6813
- DNA
Binding, 77-6727, 77-6735
Metabolism, 77-6726
Nucleosides, Embryo, Mouse, 77-6723
- DNA Repair
Diol Epoxides, 77-6724
- Environmental Hazard
Food-Chain Transfer, 77-6796
- Fetus
Metabolism, Mouse, 77-6733
- Fibroblasts
Cell Survival, 77-6731
Metabolism, Embryo, 77-6739
- Fibrosarcoma
Transplantation Immunology, 77-7068
- Guanosine, 2'-Deoxy-
Adduct Formation, 77-6724
DNA Repair, 77-6724
- Hydroxylases
Metabolism, Pancreas, 77-6741
- Hyperplasia
Epidermis, Mouse, 77-6722
- Immunity, Cellular
Graft Rejection, 77-7048
- L Cells
Cell Survival, 77-6731
- Liver
Metabolism, Embryo, 77-6739
Metabolism, Mouse, 77-6733
- Lung Neoplasms
Adenoma, 77-6683
Benzene, (2-Isothiocyantoethyl)-, 77-6683
Benzene, (2-Isothiocyantomethyl)-, 77-6683
Ultrastructural Study, 77-6736
- Metabolism
Isolation and Characterization, 77-6719
Strain Difference, Mouse, 77-7144
- Microsomes
Metabolism, Pancreas, 77-6741
- Monocytes
Metabolism, 77-6740
- Neoplasms
Perylene, 77-6738
- Phenol, (1,1-Dimethylethyl)-4-methoxy-
Carcinogenic Activity, 77-6728

Benzo(a)pyrene (cont'd)

- Carcinogenic Effect, 77-6730
- Charge-Transfer Complex, 77-6728
- Free Radicals, 77-6728
- Metabolism, Liver, Mouse, 77-6730
- Piperonyl Butoxide
Metabolism, Aquatic Organisms, 77-6796
- Propane, 1,2-Epoxy-3-(*p*-nitrophenoxy)-
Transferases, 77-6732
- Salamanders
Carcinogenic Activity, Sewage Sludge, 77-6738
- Salmonella typhimurium*
Mutagenic Activity, 77-6721, 77-6795, 77-6802
77-6830
- Smoking
Carcinogen, Chemical, 77-6626
Condensate, 77-6701
- Soil
Degradation, 77-6796
- Soil Pollutants
Hungary, 77-6737
- Stomach Neoplasms
Benzene, (2-Isothiocyantoethyl)-, 77-6683
Benzene, (2-Isothiocyantomethyl)-, 77-6683
- Transferases
Intestine, Rat, 77-6732
- Virus, Herpes Saimiri
Virus Replication, 77-7004
- Benzo(a)pyrene, 7,8-Dihydro-7,8-dihydroxy-**
Skin Neoplasms
Carcinogenic Activity, Mouse, 77-6742
12-*O*-Tetradecanoylphorbol-13-acetate, 77-6742
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-**
Adenosine, 2'-Deoxy-
Binding, 77-6725
- DNA
Binding, 77-6725
- DNA, Bacterial
Adduct Formation, 77-6723
- Guanosine, 2'-Deoxy-
Binding, 77-6725
- Hyperplasia
Epidermis, Mouse, 77-6722
- Skin Neoplasms
Carcinogenic Activity, Mouse, 77-6742
12-*O*-Tetradecanoylphorbol-13-acetate, 77-6742
- Benzo(a)pyrene-1,6-dione**
DNA
Metabolism, 77-6726
- Benzo(a)pyrene-3,6-dione**
DNA
Metabolism, 77-6726
- Benzo(a)pyrene-6,12-dione**
DNA
Metabolism, 77-6726
- Benzo(a)pyrene 4,5-Oxide**
Phenol, (1,1-Dimethylethyl)-4-methoxy-
Metabolism, Liver, Mouse, 77-6730
- Benzo(a)pyrene 9,10-Oxide**
Skin Neoplasms
Carcinogenic Activity, Mouse, 77-6742
12-*O*-Tetradecanoylphorbol-13-acetate, 77-6742

- Benzo(a)pyrene 11,12-Oxide**
Skin Neoplasms
Carcinogenic Activity, Mouse, 77-6742
12-*O*-Tetradecanoylphorbol-13-acetate, 77-6742
- Benzo(a)pyrene, 9,10-Oxy-7,8,9,10-tetrahydro-**
Hyperplasia
Epidermis, Mouse, 77-6722
- Benzo(b)triphenylene**
Aryl Hydrocarbon Hydroxylases
Epidermis, Mouse, 77-6755
Skin, Mouse, 77-6689
Benz(a)anthracene, 7,12-Dimethyl-
Aryl Hydrocarbon Hydroxylases, 77-6689
Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-, 77-6689
- Benzo(e)pyrene**
Antigens, Heterogenetic
Antibody Formation, 77-7048
- Benzo(j)fluoranthene**
Smoking
Carcinogen, Chemical, 77-6626
- 7,8-Benzoflavone**
Air Pollutants
Mutagenic Activity, 77-6830
Aryl Hydrocarbon Hydroxylases
DNA, Binding, 77-6755
Epidermis, Mouse, 77-6755
Benzo(a)pyren-3-ol
Cell Survival, 77-6731
Benzo(a)pyren-6-ol
Cell Survival, 77-6731
Polycyclic Hydrocarbons
Mutagenic Activity, 77-6830
- Benzoic Acid, 2-Amino-3-hydroxy-**
o-Toluidine, 4-(*o*-Tolylazo)-
Antigen-Antibody Reactions, 77-6843
- Benzoic Acid, *p*-Mercuri-**
Spherocytosis, Hereditary
Phosphorylation, 77-7185
- Benzophenone, 4,4'-Dichloro-**
Adrenal Gland Diseases
Benz(a)anthracene, 7,12-Dimethyl-, 77-6821
- Benzyl Isothiocyanate**
see Benzene, (2-Isothiocyanatomethyl)-
- Benzylthiocyanate**
see Thiocyanic Acid, Phenylmethyl Ester
- Besnoitia jellisoni**
Cholangioma
Benzenamine, *N,N*-Dimethyl-4((3-methylphenyl)azo)-, 77-7061
Hepatoma
Benzenamine, *N,N*-Dimethyl-4((3-methylphenyl)azo)-, 77-7061
- Bianisidine**
see Benzidine, 3,3'-Dimethyl-
- Bile Duct Neoplasms**
Adenoma
- Bile Duct Neoplasms (cont'd)**
Guanidine, Methyl-, 77-6714
Nitrous Acid, Sodium Salt, 77-6714
Nitrous Acid, Sodium Salt
Guanidine, Methyl-, 77-6714
- Biogenic Amines**
Benz(a)anthracene
Rat, 77-6687
Benz(a)anthracene, 7,12-Dimethyl-
Rat, 77-6687
Cholanthrene, 3-Methyl-
Rat, 77-6687
Diet
Nitrosamines, Review, 77-6611
- Biphenyl, 4-Chloro-**
Metabolism
Rat, 77-6816
- Biphenyl, 4,4'-Dichloro-**
Metabolism
Rat, 77-6816
- Biphenyl, 2,2',4,4',5,5'-Hexachloro-**
Metabolism
Rat, 77-6816
- Biphenyl, 2,2',4,5,5'-Pentachloro-**
Metabolism
Rat, 77-6816
- 2-Biphenylamine**
Bladder Neoplasms
Dog, 77-6840
Salmonella typhimurium
Mutagenic Activity, 77-6795, 77-6840
- 4-Biphenylamine**
Bladder
Metabolism, Dog, 77-6839
- Bladder**
Acetamide, *N*-Fluoren-2-yl-
Glucuronide Metabolite, 77-6836
Metabolism, Rabbit, 77-6836
Protein, Binding, 77-6836
Acetohydroxamic Acid, *N*-Fluoren-2-yl
Metabolism, Rabbit, 77-6836
Protein, Binding, 77-6836
4-Biphenylamine
Metabolism, Dog, 77-6839
3-Dibenzofuranamine
Metabolism, Dog, 77-6839
Fluoren-2-amine
Metabolism, Dog, 77-6839
1-Naphthylamine
Metabolism, Dog, 77-6839
2-Naphthylamine
Metabolism, Dog, 77-6839
- Bladder Neoplasms**
Benzidine
Blood Proteins, 77-6853
Occupational Hazard, 77-6853
2-Biphenylamine

Bladder Neoplasms (cont'd)

- Dog, 77-6840
- Blood Proteins
 - Serum Levels, 77-6853
- Carcinoma In Situ
 - Precancerous Conditions, Review, 77-6657
- Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 - Histological Study, 77-6841
 - Rat, 77-6841
 - Ultrastructural Study, 77-6841
 - Ultrastructural Study, Rat, Review, 77-6657
- Occupational Hazard
 - Epidemiology, 77-7168
- Thiazol, 2-Formylamine-4-(5-nitro-2-furyl)-
 - Dog, 77-6840
- Urea, Methyl Nitroso-
 - Histological Study, 77-6783
 - Rat, 77-6783

Bleomycin

- Cell Transformation, Neoplastic
 - Cells, Cultured, Review, 77-6608

Blood Cells

- Cyclophosphamide
 - Chromosome Aberrations, 77-7069

Blood Proteins

- Benzidine
 - Immune Response, 77-6853
- Bladder Neoplasms
 - Benzidine, 77-6853
 - Serum Levels, 77-6853
- Carbon Tetrachloride
 - Fetal Globulins, 77-6823

Bone Marrow

- Virus, Murine Leukemia
 - Virus Replication, 77-6945

Bone Marrow Cells

- Cyclophosphamide
 - Chromosome Aberrations, 77-7069
- Leukemia, Radiation-Induced
 - Virus, Murine Leukemia, 77-6962
- Polycythemia Vera
 - Erythropoiesis, 77-7199
- Virus, Friend Murine Leukemia
 - Virus Replication, 77-6937
- Virus, Moloney Murine Leukemia
 - Virus Replication, 77-6937
- Water, Heavy
 - Chromosome Aberrations, 77-7138
 - Erythropoiesis, 77-7138

Bone Neoplasms

- Chondrosarcoma
 - Strontium Radioisotopes, 77-6884
- Fibrosarcoma
 - Strontium Radioisotopes, 77-6884
- Sarcoma, Osteogenic
 - Strontium Radioisotopes, 77-6884
- Strontium Radioisotopes
 - Iodine Radioisotopes, 77-6884
 - Thyroidectomy, 77-6884
- Tibia
 - Case Report, 77-7100
 - Histological Study, 77-7100
 - Ultrastructural Study, 77-7100

Brain Neoplasms

- Hepatoma
 - Neoplasm Metastasis, 77-7136
- Medulloblastoma
 - Virus, Polyoma, 77-6983
- Pinealoma
 - Virus, Polyoma, 77-6983
- Sarcoma, Yoshida
 - Neoplasm Metastasis, 77-7136
- Virus, Polyoma, JC
 - Carcinogenic Effect, Hamster, 77-6983

Breast Neoplasms

- Carcinoma
 - Epidemiology, 77-7149
 - Pleural Effusion, 77-7114
- Contraceptives, Oral
 - Epidemiology, Review, 77-6620
 - Precancerous Conditions, Review, 77-6620
- Dibutyl Cyclic AMP
 - Theophylline, 77-6865
- Diet
 - Epidemiology, 77-7162
- DNA Nucleotidyltransferases
 - Isolation and Characterization, 77-7190
- Estradiol
 - Body Fluids, Review, 77-6618
 - Diet, 77-7162
 - Epidemiology, Review, 77-6618
- Estrogenic Substances, Conjugated
 - Epidemiology, 77-6873
- Estrogens
 - Epidemiology, Review, 77-6620
- Genetics
 - Age Factors, 77-7113
 - Epidemiology, 77-7113
- Hormones
 - Diet, 77-7162
- Insulin
 - DNA Replication, 77-6865
 - Estradiol, 77-6865
- Neoplasm Metastasis
 - Alanine, 3-(3,4-Dihydroxyphenyl)-, 77-6619
- Neoplasms, Multiple Primary
 - Genetics, 77-7113
- Pleural Effusion
 - Epidemiology, 77-7114
- Precancerous Conditions
 - Genetics, 77-7150
- Prolactin
 - Diet, 77-7162
 - Estradiol, 77-6865
 - Receptors, Hormone, 77-6865
- Testosterone
 - Diet, 77-7162
- Theophylline
 - DNA Replication, 77-6865
- Thyroid Neoplasms
 - Epidemiology, 77-6633

Bronchi

- Benzo(a)pyrene
 - Metabolism, 77-6727
 - Organ Culture, 77-6727
- Glycoproteins
 - Smoking, 77-7092
- Organ Culture
 - Glycoproteins, 77-7092

- Bronchial Neoplasms**
Occupational Hazard
Epidemiology, 77-7168
- Burkitt's Lymphoma**
Cells, Cultured
Virus, Epstein-Barr, 77-6999
Cyclophosphamide
Chromosome Aberrations, 77-7069
Mutagenic Activity
Host-Mediated Assay, 77-7069
Virus, Epstein-Barr
Antibodies, Viral, 77-7055
Antigen-Antibody Reactions, 77-7055
Antigen-Antibody Reactions, Review, 77-6645
Antigens, Viral, 77-6998, 77-6999
Carcinogenic Potential, Review, 77-6645
Epidemiology, 77-6998
Epidemiology, Review, 77-6644
Nucleic Acid Hybridization, 77-6998
Seroepidemiology, Review, 77-6643
Virus Replication, 77-6999
- 1,3-Butadiene, 2-Chloro-**
Benz(a)anthracene, 7,12-Dimethyl-
Carcinogenic Activity, 77-6819
Benzene
Carcinogenic Activity, 77-6819
Carcinogenic Activity
Administration Route, 77-6819
Cell Transformation, Neoplastic
Animal Model, Review, 77-6601
- 1-Butanamine, N-Butyl-N-nitroso-**
Cells, Cultured
Mutagenic Activity, 77-6770
Digestive System Neoplasms
Transplacental Carcinogenesis, 77-6776
Maternal-Fetal Exchange
Hamster, 77-6776
Respiratory Tract Neoplasms
Transplacental Carcinogenesis, 77-6776
- 2,3-Butanediol, 1,4-Dimercapto-**
Benzenamine, N,N-Dimethyl-4-((3-methylphenyl)azo)-
Mitochondria, Liver, 77-6846
Oxidative Phosphorylation, 77-6846
Streptozotocin
Guanyl Cyclase, 77-6779
Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
Guanyl Cyclase, 77-6779
- 2,3-Butanedione**
Benzenamine, N,N-Dimethyl-4-((3-methylphenyl)azo)-
Mitochondria, Liver, 77-6846
Oxidative Phosphorylation, 77-6846
- Butylated Hydroxyanisole**
see Phenol, (1,1-Dimethylethyl)-4-methoxy-
- Butyric Acid**
Erythroleukemia
Cell Differentiation, 77-7179
- Butyric Acid, 2-Amino-4-(ethylthio)-**
Adenine
RNA, Transfer, Methyltransferases, 77-6789
S-Adenosylethionine
Liver, Rat, 77-6790
Barbituric Acid, 5-Ethyl-5-phenyl-
RNA, Transfer, Methyltransferases, 77-6789
- Butyric Acid, 2-Amino-4-(ethylthio)- (cont'd)**
DNA
Liver, Rat, 77-6790
Methylation, 77-6790
Methionine, S-Adenosyl-
Liver, Rat, 77-6790
RNA, Transfer, Methyltransferases
Liver, Rat, 77-6789
- Cadmium Chloride**
Diet
Hematopoietic System, 77-6811
Toxicity, Rat, 77-6811
Kidney
Ultrastructural Study, Rat, 77-6811
Liver
Ultrastructural Study, Rat, 77-6811
- Cadmium Sulfate**
Alanine Aminotransferase
Enzymatic Activity, 77-6812
Alkaline Phosphatase
Enzymatic Activity, 77-6812
Aspartate Aminotransferase
Enzymatic Activity, 77-6812
Kidney Neoplasms
Precancerous Conditions, 77-6812
Liver Neoplasms
Precancerous Conditions, 77-6812
Serum Albumin
Blood Chemical Analysis, Rat, 77-6812
Serum Globulins
Blood Chemical Analysis, Rat, 77-6812
Urea
Blood Chemical Analysis, Rat, 77-6812
- Caffeine**
Xeroderma Pigmentosum
DNA Repair, 77-6903
Ultraviolet Rays, 77-6903
- Calcinosis**
Odontogenic Cysts
Ultrastructural Study, 77-7101
Odontogenic Tumor
Ultrastructural Study, 77-7101
- Calcium**
Cells, Cultured
Biological Transport, 77-7196
Glucose
Biological Transport, 77-7196
Ionophore A23187
Lymphocytes, 77-7197
Uridine
Biological Transport, 77-7196
- Carbamic Acid, Ethyl Ester**
Lung Neoplasms
Adenoma, 77-6878, 77-6879
Plutonium Oxide, 77-6878
- Carbamic Acid, N-Methyl-N-nitroso-, Ethyl Ester**
Salmonella typhimurium
Mutagenic Activity, 77-6795
- Carbidium**
Salmonella typhimurium
Mutagenic Activity, 77-6828
- Carbon Monoxide**
Aryl Hydrocarbon Hydroxylases

- Carbon Monoxide (cont'd)**
 - Enzymatic Activity, 77-6705
- Carbon Tetrachloride**
 - Alkaline Phosphatase
 - Enzymatic Activity, 77-6823
 - Creatine Kinase
 - Enzymatic Activity, 77-6823
 - Alpha Fetoprotein
 - Blood Proteins, 77-6823
- Carbonic Anhydrase**
 - Erythroleukemia
 - Cells, Cultured, 77-7187
- Carboxy-Lyases**
 - 12-*O*-Tetradecanoylphorbol-13-acetate
 - Cell Transformation, Neoplastic, 77-6744
 - Embryo, Hamster, 77-6744
 - Enzymatic Activity, 77-6744
- Carcinogen, Chemical**
 - Bioassay
 - Report Protocols, Review, 77-6603
 - Dose-Response Study
 - Review, 77-6606
 - Environmental Hazard
 - Dose-Response Study, 77-6896
 - Esophageal Neoplasms
 - Riboflavine, 77-6666
 - Models, Mathematical
 - Dose-Response Study, 77-6605
 - Review, 77-6605
 - Statistical Analysis, 77-6604
 - Models, Theoretical
 - Dose-Response Study, 77-6606
 - Mutagenic Activity
 - Correlation, Carcinogenic Activity, Review, 77-6607
 - Neoplasms, Experimental
 - Histocompatibility Antigens, 77-7090
 - Peptide Hydrolases
 - Liver, Rat, 77-6859
 - Smoking
 - Benz(e)acephenanthrylene, 77-6626
 - Benzo(a)pyrene, 77-6626
 - Benzo(j)fluoranthene, 77-6626
 - Chrysene, 5-Methyl-, 77-6626
 - Dibenz(a,h)anthracene, 77-6626
 - Dibenz(a,j)acridine, 77-6626
 - Dibenzo(b,def)chrysene, 77-6626
 - Isolation and Characterization, 77-6626
- Carcinogen, Environmental**
 - Cell Transformation, Neoplastic
 - Mutation, Review, 77-6660
 - Risk Factor, Review, 77-6660
 - Epidemiology
 - Review, 77-6665
- Carcinoma**
 - Benz(a)anthracene, 5,6-Dihydro,5,6-epoxy-7-methyl-
 - Mouse, 77-6697
 - Breast Neoplasms
 - Epidemiology, 77-7149
 - Pleural Effusion, 77-7114
 - Cervix Neoplasms
 - Epidemiology, 77-7158
 - Colonic Neoplasms
 - Dietary Fats, 77-6797
 - Epidemiology, 77-7149
- Carcinoma (cont'd)**
 - Lymphocytes, 77-7076
 - Hodgkin's Disease
 - Case Report, 77-6895
 - IgM
 - Transplantation Immunology, 77-7036
 - Immunity, Cellular
 - Immune Response, Humoral, 77-7063
 - Immunoglobulins, Surface
 - Growth, 77-7063
 - Immune Response, Humoral, 77-7063
 - Liver Neoplasms
 - Acetamide, *N*-Fluorenyl-, 77-6801
 - Aflatoxin B1, 77-6801
 - Diethylamine, *N*-Nitroso-, 77-6801
 - Epidemiology, 77-7160
 - Ethylene, Chloro-, 77-6825
 - Fetal Globulins, 77-7160
 - Lung Neoplasms
 - Case Report, 77-7094
 - Drug Therapy, 77-6895
 - Histological Study, 77-6663, 77-7094
 - Hodgkin's Disease, 77-6895
 - Precancerous Conditions, 77-6895
 - Radiation, 77-6895
 - Review, 77-6663
 - Ultrastructural Study, 77-7094
 - Lymphocytes
 - Transplantation Immunology, 77-7036
 - Mammary Neoplasms, Experimental
 - Adenosine Triphosphatase, 77-7192
 - Cell Cycle Kinetics, 77-7175
 - Ethylene, Chloro-, 77-6624
 - Histological Study, 77-7178
 - Radiation, Ionizing, 77-6899
 - Sex Factors, Mouse, 77-7175
 - Nasopharyngeal Neoplasms
 - Epidemiology, 77-7156
 - Ultrastructural Study, 77-6996
 - Virus, Epstein-Barr, 77-6996, 77-6997, 77-7054
 - Stomach Neoplasms
 - Epidemiology, 77-7103
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6713
 - Urea, Methyl Nitroso-, 77-7142
 - Thyroid Neoplasms
 - Chromosome Aberrations, 77-6634
 - Diagnosis and Prognosis, 77-6634
 - Epidemiology, 77-6633
 - Goiter, Exophthalmic, 77-6633
 - Radiation, Ionizing, 77-6633, 77-6634, 77-6635
 - 77-6885, 77-6889, 77-6890, 77-6891
 - Review, 77-6633
 - Uterine Neoplasms
 - Estrogenic Substances, Conjugated, 77-6874
 - Virus, Herpes Simplex 2
 - Immune Response, Hamster, 77-7045
- Carcinoma, Alveolar Cell**
 - see* Carcinoma, Bronchiolar
- Carcinoma, Basal Cell**
 - Skin Neoplasms
 - Case Report, 77-7098
 - Epidemiology, 77-7172
 - Neoplasm Metastasis, 77-7098
 - Sex Factors, 77-7172
- Carcinoma, Bronchiolar**
 - Lung Neoplasms

- Carcinoma, Bronchiolar (cont'd)**
Case Report, 77-7096
Genetics, 77-7096
Histological Study, 77-7096
- Carcinoma, Bronchogenic**
Asbestos
Epidemiology, Review, 77-6627
Cytosine, 1- β -D-Arabinofuranosyl-, Monohydrochloride
DNA Nucleotidyltransferases, 77-7190
DNA Nucleotidyltransferases
Isolation and Characterization, 77-7190
Lung Neoplasms
Case Report, 77-7093
Genetics, 77-7093
Histological Study, 77-6663
Novobiocin
DNA Nucleotidyltransferases, 77-7190
- Carcinoma, Ductal**
Mammary Neoplasms, Experimental
Radiation, Ionizing, 77-6899
- Carcinoma, Epidermoid**
Cervix Neoplasms
Radiation, Ionizing, 77-6892
Cholanthrene, 3-Methyl-
Antigenic Determinants, 77-7083
Virus, C-Type RNA Tumor, 77-7083
Graft Rejection
Antigenic Determinants, 77-7083
Head and Neck Neoplasms
Immunity, Cellular, 77-7071
Lung Neoplasms
Case Report, 77-7095
Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-, 77-6814
Epidemiology, 77-7169
Histological Study, 77-7095
Plutonium Oxide, 77-6880
Smoking, 77-6663
Ultrastructural Study, 77-6736
Skin Neoplasms
Epidemiology, 77-7172
Sex Factors, 77-7172
Ultraviolet Rays, 77-6905
Stomach Neoplasms
Guanidine, 1-Ethyl-3-nitro-1-nitroso-, 77-6710
Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6710
Vaginal Neoplasms
Radiation, Ionizing, 77-6892
- Carcinoma In Situ**
Bladder Neoplasms
Precancerous Conditions, Review, 77-6657
Vaginal Neoplasms
Radiation, Ionizing, 77-6892
- Carcinoma, Oat Cell**
Lung Neoplasms
Histological Study, 77-6663
- Carcinoma, Scirrhous**
Mammary Neoplasms, Experimental
Adenosine Triphosphatase, 77-7192
- Carcinoma, Small Cell**
see Carcinoma; Carcinoma, Bronchogenic; Carcinoma, Oat Cell
- Carcinoma, Squamous Cell**
see Carcinoma, Epidermoid
- Carcinoma 256, Walker**
Kallikrein-Trypsin Inactivator
Immune Response, 77-7180
Neoplasm Metastasis, 77-7180
Lung Neoplasms
Neoplasm Metastasis, 77-7180
- Carrier Proteins**
Virus, C-Type RNA Tumor
RNA, Viral, 77-6932
Virus, Rous Sarcoma
RNA, Viral, 77-6932
- Cartilage**
Virus, Rous Sarcoma
Acetic Acid, 77-6929
Cell Transformation, Neoplastic, 77-6929
Glucose, 2-Deoxy-, 77-6929
Hyaluronic Acid, 77-6929
Mucopolysaccharides, 77-6928
- Catalase**
Liver Neoplasms
Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-, 77-6845
- Cecal Neoplasms**
DNA Nucleotidyltransferases
Isolation and Characterization, 77-7190
- Cell Adhesion**
Fibrin
Cells, Cultured, 77-7183
Hexanoic Acid, 6-Amino-, 77-7183
Virus, Rous Sarcoma
Cell Transformation, Neoplastic, 77-6925
Fibroblasts, 77-6925
- Cell Aggregation**
Cell Transformation, Neoplastic
Anchorage Dependence, 77-7182
Fibroblasts, 77-6981
Teratoid Tumor
Plasminogen, 77-7147
Virus, Shope Rabbit Fibroma
Ultraviolet Rays, 77-6939
Virus Replication, 77-6939
Virus, SV40
Hybrid Cells, 77-7010
- Cell Differentiation**
Aminotransferases
Isoenzymes, 77-7015
Benz(a)anthracene, 7,12-Dimethyl-
Cells, Cultured, 77-6686
Dimethylamine, *N*-Nitroso-
Cells, Cultured, 77-6773
Kidney, Rat, 77-6773
Erythroleukemia
Acetamide, *N,N*-Dimethyl-, 77-7179
Butyric Acid, 77-7179
Methane, Sulfinylbis-, 77-7179
Leukemia, Hairy Cell
Lymphocytes, 77-7132
Leukemia, Myelocytic
Chromosome Aberrations, 77-7127
Karyotyping, 77-7127
Nephroblastoma

Cell Differentiation (cont'd)

- Cells, Cultured, 77-7111
- Tissue, Embryonic, 77-7111
- Phorbol
 - Cells, Cultured, 77-6748
- Phorbol-12,13-diacetate
 - Cells, Cultured, 77-6748
- Phorbol-12,13-dibenzoate
 - Cells, Cultured, 77-6748
 - Lipids, 77-6748
- Phorbol-12,13-didecanoate
 - Cells, Cultured, 77-6748
- 4 α -Phorbol-12,13-didecanoate
 - Cells, Cultured, 77-6748
 - Lipids, 77-6748
- Smoking
 - Lung, Chicken, 77-6704
 - Mesenchyma, 77-6704
- Teratoid Tumor
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-7044
 - Plasminogen, 77-7147
 - Radiation, Ionizing, 77-7044
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Cell Transformation, Neoplastic, 77-6745
 - Cells, Cultured, 77-6748
 - Lipids, 77-6748
- Virus, Friend Murine Leukemia
 - Hematopoietic Stem Cells, 77-6937
- Virus, Moloney Murine Leukemia
 - Hematopoietic Stem Cells, 77-6937
- Virus, Rauscher Murine Leukemia
 - Hematopoietic Stem Cells, 77-6950

Cell Division

- Methanol, (Methyl-*ONN*-azoxy)-
 - Intestine, Rat, 77-6863

Cell Fusion

- Cell Transformation, Neoplastic
 - Mitosis, Review, 77-6654
 - Somatic Cells, Review, 77-6654
- Virus Activation
 - Somatic Cells, Review, 77-6654

Cell Membrane

- Adenosine Triphosphatase
 - Cell Cycle Kinetics, 77-6750
- Cell Transformation, Neoplastic
 - Glycopeptides, 77-6971
 - Proteins, Review, 77-6654
- Hepatoma
 - Glycopeptides, 77-6971
- Mammary Neoplasms, Experimental
 - Adenosine Triphosphatase, 77-7192
- Peptide Hydrolases
 - Cell Transformation, Neoplastic, 77-6859
- Sarcoma
 - DNA Replication, 77-7189
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Cell Cycle Kinetics, 77-6750
- Virus, Epstein-Barr
 - Antigens, Viral, 77-6995
- Virus, Feline Leukemia
 - Antigens, Viral, 77-7082
- Virus, Polyoma
 - Antigens, Neoplasm, 77-6979
 - Viral Proteins, 77-6979
- Virus, Rous Sarcoma
 - Binding Sites, 77-6917

Cell Membrane (cont'd)

- Proteins, 77-6925
- Trypsin, 77-6917

Cell Movement

- Lymphocytes
 - Ovalbumin, 77-7080
 - Serum Albumin, 77-7080

Cell Transformation, Neoplastic

- Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 - Histological Study, Hamster, 77-6793
- Acetamide, *N*-Fluoren-2-yl-
 - Animal Model, Review, 77-6601
- Acetamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 - Cells, Cultured, 77-6842
- Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-
 - Cells, Cultured, 77-6842
- Actinomycin D
 - Cells, Cultured, Review, 77-6608
- Adriamycin
 - Cells, Cultured, Review, 77-6608
- Aflatoxin B1
 - Histological Study, Hamster, 77-6793
- Aminotransferases
 - Isoenzymes, 77-7015
- Benz(a)anthracene, 7,12-Dimethyl-
 - Cells, Cultured, 77-6686
 - Contact Inhibition, 77-7144
 - Strain Difference, Mouse, 77-7144
 - Submandibular Gland, 77-6686
- Benzo(a)pyrene
 - Histological Study, Hamster, 77-6793
- Biological Transport
 - Ultrastructural Study, 77-6931
- Bleomycin
 - Cells, Cultured, Review, 77-6608
- 1,3-Butadiene, 2-Chloro-
 - Animal Model, Review, 77-6601
- Carcinogen, Environmental
 - Mutation, Review, 77-6660
 - Risk Factor, Review, 77-6660
- Cell Aggregation
 - Anchorage Dependence, 77-7182
- Cell Fusion
 - Mitosis, Review, 77-6654
 - Somatic Cells, Review, 77-6654
- Cell Membrane
 - Proteins, Review, 77-6654
- Cholanthrene, 3-Methyl-
 - DNA Replication, 77-6680
 - Histological Study, Hamster, 77-6793
- Chromosome Aberrations
 - Leukemia, Myelocytic, 77-7127
- Coal Tar
 - Animal Models, Review, 77-6602
- Colonic Neoplasms
 - Fibroblasts, 77-6652
 - Virus, Kirsten Murine Sarcoma, 77-6652
- Cytosine, 1- β -*D*-Arabinofuranosyl-, Monohydrochloride
 - Cells, Cultured, Review, 77-6608
- Daunomycin
 - Cells, Cultured, Review, 77-6608
- Dibenz(a,h)anthracene
 - Histological Study, Hamster, 77-6793
- Dimethylamine, *N*-Nitroso-
 - Cells, Cultured, 77-6773
 - Kidney, Rat, 77-6773

Cell Transformation, Neoplastic (cont'd)

- Diphenylamine, *N*-Nitroso-
 - Cells, Cultured, 77-6760
- Ether, Bis(chloromethyl)-
 - Animal Model, Review, 77-6601
- Ethylene, Chloro-
 - Animal Model, Review, 77-6601
 - Cells, Cultured, 77-6760
- Ethylene, 1,1-Dichloro-
 - Animal Model, Review, 77-6601
- Fibroblasts
 - Cell Aggregation, 77-6981
- Folic Acid, *N*-Nitroso-
 - Cells, Cultured, 77-6760
- Food Additives
 - Ethylene, 1,1-Dichloro-, 77-6601
- Foreign Body Reaction
 - Mouse, 77-6909
- Furan, 2-Methyl-5-nitro-
 - Cells, Cultured, 77-6842
- Galactosyltransferases
 - Animal Model, Hamster, 77-6980
- Genetics
 - Mutation, Review, 77-6660
 - Risk Factor, Review, 77-6660
- Glycopeptides
 - Cell Membrane, 77-6971
 - Epithelial Cells, 77-6971
 - Fucose, 77-6971
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Contact Inhibition, 77-7144
 - Histological Study, Hamster, 77-6793
 - Strain Difference, Mouse, 77-7144
- Heparin
 - Mouse, 77-6973
- Herbicides
 - Animal Model, Review, 77-6601
- IgG
 - Solid Tumors, Review, 77-6651
- IgM
 - Solid Tumors, Review, 77-6651
- Immunoglobulins
 - Solid Tumors, Review, 77-6651
- Isolation and Characterization
 - Histological Study, 77-7145
- Lymphocytes
 - Immune Response, 77-6648
- Methanesulfonic Acid, Ethyl Ester
 - Histological Study, Hamster, 77-6793
- Methanesulfonic Acid, Methyl Ester
 - Histological Study, Hamster, 77-6793
- Methotrexate
 - Cells, Cultured, Review, 77-6608
- Mitomycin C
 - Lymphocytes, 77-7070
- Morpholine, *N*-Nitroso-
 - Glycogenesis, 77-6709
- 2-Oxetanone
 - Histological Study, Hamster, 77-6793
- Peptide Hydrolases
 - Cell Membrane, 77-6859
 - Liver, Rat, 77-6859
- Pesticides
 - Animal Model, Review, 77-6601
- Quinoline, 4-Nitro-, 1-Oxide
 - Contact Inhibition, 77-7144
 - DNA Repair, 77-6858

Cell Transformation, Neoplastic (cont'd)

- Strain Difference, Mouse, 77-7144
- Virus, Rauscher Murine Leukemia, 77-6858
- Serum Albumin
 - Solid Tumors, Review, 77-6651
- Serum Globulins
 - Solid Tumors, Review, 77-6651
- Smoking
 - Animal Model, Review, 77-6602
- 4,4'-Stilbenediol, α, α' -Diethyl-
 - Animal Model, Review, 77-6602
- Submandibular Gland
 - Cells, Cultured, 77-6686
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Carboxy-Lyases, 77-6744
 - Cell Differentiation, 77-6745
 - DNA Replication, 77-6744
- o*-Toluidine, 4-(*o*-Tolylazo)-
 - Antigen-Antibody Reactions, 77-6843
- Uracil, 5-(Bis(2-chloroethyl)amino)-
 - Cells, Cultured, Review, 77-6608
- Uracil, 5-Fluoro-
 - Cells, Cultured, Review, 77-6608
- Urea, Hydroxy-
 - Cells, Cultured, Review, 77-6608
- Urea, Methyl Nitroso-
 - Fetus, Hamster, 77-6784
 - Neuroglia, 77-6784
- Uridine, 2'-Deoxy-5-fluoro-
 - Cells, Cultured, Review, 77-6608
- Virus, Adeno 12
 - DNA, Viral, 77-6988
- Virus, Avian Sarcoma
 - DNA, Viral, 77-6921
- Virus, B77
 - Antigenic Determinants, 77-6972
 - Viral Proteins, 77-6972
- Virus, C-Type RNA Tumor
 - Antigens, Viral, 77-6966
- Virus, Feline Leukemia
 - Antigens, Viral, 77-6934
- Virus, Feline Sarcoma
 - Antigens, Viral, 77-6934
- Virus, Friend Murine Leukemia
 - Erythropoiesis, 77-6956
- Virus, Herpes Simplex 1
 - Viral Proteins, 77-7000
- Virus, Kirsten Murine Sarcoma
 - Adenoma, 77-6974
 - Fibroblasts, 77-6974
 - Glycolipids, 77-7057
 - Heparin, 77-6973
- Virus, Moloney Murine Sarcoma
 - Viral Proteins, 77-6969
- Virus, Murine Leukemia
 - Mouse, AKR, 77-6963
- Virus, Murine Mammary Tumor
 - Thymus Gland, 77-7066
- Virus, Papova
 - Isolation and Characterization, 77-7008
- Virus, Polyoma
 - Aminotransferases, 77-7015
 - Fibroblasts, 77-6981
 - Temperature Sensitive Mutants, 77-6977
 - Viral Proteins, 77-6979
- Virus, Polyoma, BK
 - DNA, Viral, 77-6982

Cell Transformation, Neoplastic (cont'd)

Virus, Rous Sarcoma

- Aminotransferases, 77-7015
- Biological Transport, 77-6931
- Cartilage, 77-6929
- Cell Adhesion, 77-6925
- Chick Embryo, 77-6930
- Chondroitin, 77-6928
- Glucose, 77-6927
- Karyotyping, 77-6930
- Mucopolysaccharides, 77-6928
- Proteins, 77-6925
- Temperature Sensitive Mutants, 77-6925, 77-6929

Virus, SV40

- Antigens, Neoplasm, 77-7070
- Ataxia Telangiectasia, 77-7019
- Chromosomes, Human, 16-18, 77-7011
- DNA Replication, 77-7022
- Fibroblasts, 77-7139
- Heparin, 77-6973
- Histocompatibility Antigens, 77-7070
- Hybrid Cells, 77-7010, 77-7011, 77-7013, 77-7141
- Phenotype, 77-7010
- Temperature Sensitive Mutants, 77-7026
- Viral Proteins, 77-7027

Cells, Cultured

Acetamide, *N*-(Carbamoylmethyl)-2-diazo-

- Chromatids, 77-6850
- DNA Repair, 77-6850

Acetamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-

- Cell Transformation, Neoplastic, 77-6842

Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-

- Cell Transformation, Neoplastic, 77-6842

Adenosine Cyclic 3',5' Monophosphate

- Hepatoma, 77-7193

Aflatoxin B1

- DNA Replication, 77-6667

Arsenious Acid, Sodium Salt

- Cell Survival, 77-6810

Benz(a)anthracene

- Mutagenic Activity, 77-6721

Benz(a)anthracene, 7,12-Dimethyl-

- Cell Transformation, Neoplastic, 77-6686

Benzo(a)pyren-3-ol

- Cell Survival, 77-6731
- Metabolism, 77-6729

Benzo(a)pyren-6-ol

- Cell Survival, 77-6731

Benzo(a)pyren-9-ol

- Metabolism, 77-6729

Benzo(a)pyrene

- Histological Study, 77-6734
- Metabolism, 77-6729
- Metabolism, Embryo, 77-6739
- Mutagenic Activity, 77-6721

Burkitt's Lymphoma

- Virus, Epstein-Barr, 77-6999

Calcium

- Biological Transport, 77-7196

Cell Differentiation

- Benz(a)anthracene, 7,12-Dimethyl-, 77-6686

Chondrosarcoma

- Karyotyping, 77-6990
- RNA, Viral, 77-6990
- Sex Chromosomes, 77-6990

Chromosome Aberrations

- Ataxia Telangiectasia, 77-7019

Cells, Cultured (cont'd)

Chromosomes

- Embryo, Mouse, 77-7144

Contact Inhibition

- Embryo, Mouse, 77-7144

Dimethylamine, *N*-Nitroso-

- Cell Differentiation, 77-6773
- Cell Transformation, Neoplastic, 77-6773
- Kidney, Rat, 77-6773
- Mutagenic Activity, 77-6772

Diphenylamine, *N*-Nitroso-

- Cell Transformation, Neoplastic, 77-6760

DNA Repair

- Xeroderma Pigmentosum, 77-6792

Erythroleukemia

- Carbonic Anhydrase, 77-7187

Ethylene, Chloro-

- Cell Transformation, Neoplastic, 77-6760

Fibrin

- Cell Adhesion, 77-7183
- Fibrinolysis, 77-7183

Fibrosarcoma

- Migration Inhibitory Factor, 77-7059

Folic Acid, *N*-Nitroso-

- Cell Transformation, Neoplastic, 77-6760

Furan, 2-Methyl-5-nitro-

- Cell Transformation, Neoplastic, 77-6842

Glucose, 2-Deoxy-

- Glycoproteins, 77-7181
- Toxicology, 77-7181

Guanosine Cyclic 3',5' Monophosphate

- Hepatoma, 77-7193

Leukemia, Myeloblastic

- Review, 77-6642

Leukemia, Myelocytic

- Review, 77-6642

Lymphosarcoma

- Pig, 77-7124
- Virus-Like Particles, C-Type, 77-7124

Magnesium

- Biological Transport, 77-7196

Nephroblastoma

- Cell Differentiation, 77-7111

Phorbol

- Cell Differentiation, 77-6748
- Mutagenic Activity, Hamster, 77-6746

Phorbol-12,13-diacetate

- Cell Differentiation, 77-6748

Phorbol-12,13-dibenzoate

- Cell Differentiation, 77-6748

Phorbol-12,13-didecanoate

- Cell Differentiation, 77-6748

4 α -Phorbol-12,13-didecanoate

- Cell Differentiation, 77-6748

Quinoline, 4-Nitro-, 1-Oxide

- Chromosome Aberrations, 77-6861
- DNA Repair, 77-6792
- DNA Replication, 77-6861

Smoking

- Isoenzymes, 77-6700

Submandibular Gland

- Cell Transformation, Neoplastic, 77-6686

Sulfuric Acid, Dimethyl Ester

- DNA Repair, 77-6792

Teratoid Tumor

- Plasminogen, 77-7147

12-*O*-Tetradecanoylphorbol-13-acetate

Cells, Cultured (cont'd)

- Cell Differentiation, 77-6748
- Ultraviolet Rays
 - Mutagenic Activity, Hamster, 77-6746
- Urea, Ethyl Nitroso-
 - Chromosome Aberrations, 77-6785
 - DNA Repair, 77-6792
- Urea, Methyl Nitroso-
 - DNA Repair, 77-6792
- Virus, Avian Myeloblastosis
 - Peptides, 77-6926
- Virus, D-Type RNA Tumor
 - Isolation and Characterization, Review, 77-6638
- Virus, Feline Leukemia
 - Antigens, Viral, 77-6935, 77-6957
 - RNA, Viral, 77-6935
 - Virus Replication, 77-6935
- Virus, Friend Murine Leukemia
 - Antigens, Viral, 77-6957, 77-6958
- Virus, Gibbon Ape Lymphoma
 - Antigens, Viral, 77-6957
- Virus, Gross Murine Leukemia
 - Antigens, Viral, 77-6957
- Virus, Moloney Murine Leukemia
 - Antigens, Viral, 77-6957
- Virus, Murine Mammary Tumor
 - Dexamethasone, 77-6942
 - Hepatoma, 77-6942
- Virus, Rauscher Murine Leukemia
 - Antigens, Viral, 77-6957
- Virus, Rous Sarcoma
 - Peptides, 77-6926
- Virus, Shope Rabbit Fibroma
 - Virus Replication, 77-6939

Cellular Inclusions

- Leukemia, Lymphocytic
 - Case Report, 77-7131
 - Immunoglobulins, 77-7131
 - Ultrastructural Study, 77-7131

Cellulose, Methyl Ether

- L Cells
 - Hybrid Cells, 77-7037

Cervix Neoplasms

- Carcinoma
 - Epidemiology, 77-7158
- Carcinoma, Epidermoid
 - Radiation, Ionizing, 77-6892
- Estrogenic Substances, Conjugated
 - Case Report, 77-7115
 - Histological Study, 77-7115

Chemotaxis

- Corynebacterium parvum*
 - Monocytes, 77-7058
 - Neutrophils, 77-7058
- Fibrosarcoma
 - Leukocytes, 77-7059
 - Macrophages, 77-7059
- Lymphocytes
 - Ovalbumin, 77-7080
 - Serum Albumin, 77-7080
- Macrophages
 - Mycobacterium bovis*, 77-7059
- Pyran
 - Monocytes, 77-7058
 - Neutrophils, 77-7058

Chloramphenicol

- DNA
 - L(+) and D(-) Isomers, 77-6829
- Escherichia coli*
 - DNA, 77-6829
 - Mutagenic Activity, 77-6829
- Salmonella typhimurium*
 - DNA, 77-6829
 - Mutagenic Activity, 77-6829

Chloroprene

- see 1,3-Butadiene, 2-Chloro-

Cholangiocarcinoma

- see Cholangioma

Cholangioma

- Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-*Besnoitia jellisoni*, 77-7061
- Toxoplasma gondii*, 77-7061
- Liver Neoplasms
 - Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-, 77-6814

Cholanthrene, 3-Methyl-

- Acetic Acid, (2,3-Dichloro-4-(2-methylenebutyl)phenoxy)-
 - Transferases, 77-6732
- Acetohydroxamic Acid, *N*-Fluorenyl-
 - Hydroxylases, 77-6833
- Aryl Hydrocarbon Hydroxylases
 - Enzymatic Activity, 77-6752
 - Liver, Mouse, 77-6754
 - Liver, Rat, 77-6751
 - Strain Difference, Mouse, 77-6754
- Benzene, 1-Chloro-2,4-dinitro-
 - Transferases, 77-6732
- Benzene, 1-(Chloromethyl)-4-nitro-
 - Transferases, 77-6732
- Benzo(a)pyrene
 - Metabolism, Pancreas, 77-6741
- Biogenic Amines
 - Rat, 77-6687
- Carcinoma, Epidermoid
 - Antigenic Determinants, 77-7083
 - Virus, C-Type RNA Tumor, 77-7083
- Cell Transformation, Neoplastic
 - Histological Study, Hamster, 77-6793
- Dexamethasone
 - Aryl Hydrocarbon Hydroxylases, 77-6755
 - DNA, Binding, 77-6755
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
 - Aryl Hydrocarbon Hydroxylases, 77-6754
 - Glucosyltransferases, 77-6754
- Dimethylamine, *N*-Nitroso-
 - Mutagenic Activity, 77-6770
- DNA Replication
 - Cell Transformation, Neoplastic, 77-6680
- Epoxide Hydratases
 - Enzymatic Activity, 77-6753
- Fibrosarcoma
 - Migration Inhibitory Factor, 77-7059
- Glucosyltransferases
 - Liver, Mouse, 77-6754
 - Strain Difference, Mouse, 77-6754
- Indole-3-acetic Acid, 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methyl-
 - Aryl Hydrocarbon Hydroxylases, 77-6755
- Leukemia, Myelocytic
 - Chromosome Aberrations, 77-7130

Cholanthrene, 3-Methyl- (cont'd)

- Lymph Nodes
 - DNA Replication, 77-6680
- Lymphocytes
 - DNA Replication, 77-6680
- Mitochondria
 - Oxidative Phosphorylation, 77-6800
- Neoplasms, Experimental
 - Ascorbic Acid, 77-6679
 - Listeria monocytogenes*, 77-7047
 - Sarcoma, 77-7047
- Nicotine
 - Metabolism, 77-6705
- Orotic Acid
 - Microsomes, Liver, 77-6678
- Propane, 1,2-Epoxy-3-(*p*-nitrophenoxy)-
 - Transferases, 77-6732
- 3,5-Pyrazolidinedione, 4-Butyl-1-(*p*-hydroxyphenyl)-2-phenyl-
 - Aryl Hydrocarbon Hydroxylases, 77-6755
 - DNA, Binding, 77-6755
- RNA, Ribosomal
 - Liver, Rat, 77-6678
- Sarcoma
 - Antigens, 77-7086
 - Hybrid Cells, 77-7087
 - Immunity, 77-7086
- Seclazone
 - Aryl Hydrocarbon Hydroxylases, 77-6755
- Skin Neoplasms
 - Dexamethasone, 77-6755
 - Indole-3-acetic acid, 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methyl-, 77-6755
 - 3,5-Pyrazolidinedione, 4-Butyl-1-(*p*-hydroxyphenyl)-2-phenyl-, 77-6755
 - Seclazone, 77-6755
- Transferases
 - Intestine, Rat, 77-6732
- Virus, Herpes Saimiri
 - Virus Replication, 77-7004

Choline Acetate (Ester)

- Digestive System Neoplasms
 - Neural Transmission, Review, 77-6653

Chondroitin

- Virus, Rous Sarcoma
 - Cell Transformation, Neoplastic, 77-6928

Chondrosarcoma

- Bone Neoplasms
 - Strontium Radioisotopes, 77-6884
- Cells, Cultured
 - Karyotyping, 77-6990
 - RNA, Viral, 77-6990
 - Sex Chromosomes, 77-6990
- Virus, C-Type RNA Tumor
 - RNA, Viral, 77-6990
 - Virus-Like Particles, 77-6990

Chromatids

- Acetamide, *N*-(Carbamoylmethyl)-2-diazo-
 - Cells, Cultured, 77-6850

Chromatin

- Erythroleukemia
 - Methane, Sulfinylbis-, 77-7179
- Virus, SV40
 - Cell-Free Assembly, 77-7028
 - Chromosomes, 77-7029

Chromatin (cont'd)

- DNA, Viral, 77-7028

Chromic Acid

- Chromosome Aberrations
 - Occupational Hazard, 77-6803
- Lymphocytes
 - Chromosome Aberrations, 77-6803

Chromium Oxide

- Chromosome Aberrations
 - Occupational Hazard, 77-6803
- Lymphocytes
 - Chromosome Aberrations, 77-6803

Chromosome Aberrations

- Ataxia Telangiectasia
 - Cells, Cultured, 77-7019
- Burkitt's Lymphoma
 - Cyclophosphamide, 77-7069
- Chromic Acid
 - Lymphocytes, 77-6803
 - Occupational Hazard, 77-6803
- Chromium Oxide
 - Lymphocytes, 77-6803
 - Occupational Hazard, 77-6803
- Cyclophosphamide
 - Blood Cells, 77-7069
 - Bone Marrow Cells, 77-7069
- Dichromic Acid, Dipotassium Salt
 - Fibroblasts, 77-6803
- Dichromic Acid, Disodium Salt
 - Lymphocytes, 77-6803
 - Occupational Hazard, 77-6803
- Ethyl Alcohol
 - Leukocytes, Review, 77-6610
- Ethylene, Chloro-
 - Epidemiology, 77-6827
- Leukemia, Lymphoblastic
 - Case Report, 77-7129
- Leukemia, Myeloblastic
 - Case Report, 77-7129
- Leukemia, Myelocytic
 - Cell Differentiation, 77-7127
 - Cell Transformation, Neoplastic, 77-7127
 - Cholanthrene, 3-Methyl-, 77-7130
 - G-Banding, 77-7130
 - Mitosis, 77-7130
- Plutonium
 - Lung, 77-6881
- Quinoline, 4-Nitro-, 1-Oxide
 - Cells, Cultured, 77-6861
 - Species Difference, 77-6861
- Radiation, Ionizing
 - Lymphocytes, 77-6902
- Thyroid Neoplasms
 - Carcinoma, 77-6634
 - Thyrotropin, 77-6634
- Urea, Ethyl Nitroso-
 - Cells, Cultured, 77-6785
- Water, Heavy
 - Bone Marrow Cells, 77-7138
 - Precancerous Conditions, 77-7138

Chromosome Abnormalities

- Hepatoma
 - Aniline, 2,4,6-Trimethyl-, 77-6849
- Intestinal Neoplasms
 - Genetics, 77-7105

Chromosome Abnormalities (cont'd)

- Leukemia
 - Precancerous Conditions, 77-6659
- Pituitary Neoplasms
 - Aniline, 2,4,6-Trimethyl-, 77-6849
- Polyps
 - Genetics, 77-7105

Chromosomes

- Ataxia Telangiectasia
 - Virus, SV40, 77-7139
- Cells, Cultured
 - Embryo, Mouse, 77-7144
- Glioma
 - Urea, Ethyl Nitroso-, 77-7137
- Mammary Neoplasms, Experimental
 - Hybrid Cells, 77-7087
- Neurilemmoma
 - Urea, Ethyl Nitroso-, 77-7137
- Neurofibroma
 - Virus, SV40, 77-7139
- Oligodendroglioma
 - Urea, Ethyl Nitroso-, 77-7137
- Precancerous Conditions
 - Virus, SV40, 77-7139
- Sarcoma
 - Hybrid Cells, 77-7087
- Virus, SV40
 - Chromatin, 77-7029
 - DNA, Viral, 77-7029, 77-7139
 - Isolation and Characterization, 77-7029

Chromosomes, Human, 6-12

- Virus, SV40
 - Hybrid Cells, 77-7010

Chromosomes, Human, 16-18

- Virus, SV40
 - Cell Transformation, Neoplastic, 77-7011
 - Hybrid Cells, 77-7011

Chromosomes, Human, 21-22

- Leukemia, Myelocytic
 - Macrophages, 77-7128
 - Mitosis, 77-7128

Chrysene, 5-Methyl-

- Smoking
 - Carcinogen, Chemical, 77-6626

Clostridium perfringens

- Fluoren-2-amine
 - Carcinogenic Metabolite, 77-6831

Coal Tar

- Cell Transformation, Neoplastic
 - Animal Models, Review, 77-6602

Coke

- Lung Neoplasms
 - Epidemiology, 77-7170

Collagen

- Fibrosarcoma
 - Neoplasm Circulating Cells, 77-7146

Colonic Neoplasms

- Adenocarcinoma
 - Histological Study, 77-6712, 77-6856
 - Ultrastructural Study, 77-6856
- Adenoma
 - Dietary Fats, 77-6797

Colonic Neoplasms (cont'd)

- Histological Study, 77-6712
- Adenomatosis, Familial Endocrine
 - Phenotypic Markers, Review, 77-6652
- Asbestos
 - Epidemiology, 77-6914
- Carcinoma
 - Dietary Fats, 77-6797
 - Epidemiology, 77-7149
 - Lymphocytes, 77-7076
- Diet
 - Epidemiology, 77-7164
- Fibroblasts
 - Cell Transformation, Neoplastic, 77-6652
- Genetics
 - Case Report, 77-7151
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Adenocarcinoma, 77-6712
 - Adenoma, 77-6712
 - Bile Acids and Salts, 77-6712
- Hydrazine, 1,2-Dimethyl-
 - Adenocarcinoma, 77-6856
 - Carcinogenic Potential, 77-6855
 - Dietary Fats, 77-6797
 - Genetics, 77-6855
 - Ultrastructural Study, 77-6857
- Methane, Azoxy-
 - Rat, 77-6864
- Methanol, (Methyl-*ONN*-azoxy)-, Acetate
 - Dietary Fats, 77-6797
- Urea, Methyl Nitroso-
 - Dietary Fats, 77-6797
- Virus, Kirsten Murine Sarcoma
 - Cell Transformation, Neoplastic, 77-6652
 - Genetics, 77-6974

Complement

- Leukemia, Hairy Cell
 - Lymphocytes, 77-7132
- Leukemia, Myelocytic
 - Karyotyping, 77-7127

Concanavalin A

- Head and Neck Neoplasms
 - Lymphocytes, 77-7071
- Hepatoma
 - Binding, 77-7191
 - D*-Mannopyranoside, α -Methyl-, 77-7191
 - Tyrosine Aminotransferase, 77-7191
- Leukemia L1210
 - Immune Response, 77-7040
- Lymphocytes
 - Virus, Bovine Leukemia, 77-6938
- Lymphosarcoma
 - Virus, Bovine Leukemia, 77-6938
- Virus, Herpes Simplex 1
 - Viral Proteins, 77-7000

Contact Inhibition

- Benz(a)anthracene, 7,12-Dimethyl-
 - Cell Transformation, Neoplastic, 77-7144
- Cells, Cultured
 - Embryo, Mouse, 77-7144
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Cell Transformation, Neoplastic, 77-7144
- Quinoline, 4-Nitro-, 1-Oxide
 - Cell Transformation, Neoplastic, 77-7144

Contraceptives, Oral

Breast Neoplasms

Epidemiology, Review, 77-6620

Precancerous Conditions, Review, 77-6620

Hepatosoma

Epidemiology, 77-7159

Epidemiology, Review, 77-6621

Review, 77-6622

Liver Neoplasms

Adenoma, 77-7110

Dose-Response Study, 77-7159

Epidemiology, 77-7159

Hamartoma, 77-6621

Hyperplasia, 77-6621

Mouse, 77-6866

Precancerous Conditions, 77-7159

opper Sulfate Pentahydrate

Testicular Neoplasms

Disgerminoma, 77-6806

Gonadotropins, Pituitary, 77-6806

Teratoid Tumor, 77-6806

rynebacterium parvum

Monocytes

Chemotaxis, 77-7058

Neutrophils

Chemotaxis, 77-7058

umarin

Cytochrome P-450

Metabolism, Liver, 77-6813

umarin, 7-Ethoxy-

Cytochrome P-450

Metabolism, Liver, 77-6813

eatine Kinase

Carbon Tetrachloride

Enzymatic Activity, 77-6823

resol, 2,6-Di-*tert*-butyl-

Liver Neoplasms

Acetamide, *N*-Fluoren-2-yl-, 77-6837

roglobulins

Multiple Myeloma

Ultrastructural Study, 77-7122

lohexane, 1,2,3,4,5,6-Hexachloro-, α -Isomer

Dietary Proteins

Liver, Rat, 77-6818

DNA Replication

Cell Cycle Kinetics, 77-6818

Liver, Rat, 77-6818

loheximide

Fibrinogen

Liver, Rat, 77-7184

Proteins

Liver, Rat, 77-7184

Virus, SV40

DNA Replication, 77-7022

lophosphamide

Blood Cells

Chromosome Aberrations, 77-7069

Bone Marrow Cells

Chromosome Aberrations, 77-7069

Burkitt's Lymphoma

Chromosome Aberrations, 77-7069

Leukemia, Myelocytic

Cyclophosphamide (cont'd)

Lymphoma, 77-7126

Virus, Harvey Murine Sarcoma

Carcinogenic Activity, 77-6970

Dose-Response Study, 77-6970

Cystadenocarcinoma

Liver Neoplasms

Case Report, 77-7106

Histological Study, 77-7106

Cystadenoma

Liver Neoplasms

Case Report, 77-7106

Histological Study, 77-7106

Cysteine

Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-

Guanyl Cyclase, 77-6779

Cytochrome P-450

Acetanilide

Metabolism, Liver, 77-6813

Antipyrine, 4-(Dimethylamino)-

Metabolism, Liver, 77-6813

Benzo(a)pyrene

Metabolism, Liver, 77-6813

Coumarin

Metabolism, Liver, 77-6813

Coumarin, 7-Ethoxy-

Metabolism, Liver, 77-6813

Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-

Microsomes, Liver, 77-6813

Dimethylamine, *N*-Nitroso-

Metabolism, Rat, 77-6774

Ethane, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)-

Liver, Rat, 77-6822

Kepone

Liver, Rat, 77-6820

Microsomes, Liver

Oxygenases, 77-6813

Nutrition

Mixed Function Oxidases, 77-6614

Cytochrome Reductases

Kepone

Liver, Rat, 77-6820

Cytosine, 1- β -*D*-Arabinofuranosyl-, Monohydrochloride

Carcinoma, Bronchogenic

DNA Nucleotidyltransferases, 77-7190

Cell Transformation, Neoplastic

Cells, Cultured, Review, 77-6608

DNA Nucleotidyltransferases

Liver Regeneration, 77-7190

Virus, Herpes Simplex 1

Virus Replication, 77-7002

Cytosine Nucleotides

Sarcoma

DNA Replication, 77-7189

D-T Diaphorases

see Quinone Reductases

Daunomycin

Cell Transformation, Neoplastic

Cells, Cultured, Review, 77-6608

- p,p*-DDT**
 see Ethane, 1,1-Dichloro-2,3-bis(*p*-chlorophenyl)-
- 1-Decanaminium, *N,N,N*-Trimethyl-, Bromide**
 1-Hexanamine, *N*-Hexyl-
 Nitrosation Kinetics, 77-6763
 Nitrous Acid, 77-6763
- Decyltrimethylammonium Bromide**
 see 1-Decanaminium, *N,N,N*-Trimethyl-, Bromide
- Deoxyribonuclease**
 Sarcoma
 DNA Replication, 77-7189
- Deoxyribonucleosides**
 Urea, Hydroxy-
 DNA Replication, 77-6787
- Dexamethasone**
 Cholanthrene, 3-Methyl-
 Aryl Hydrocarbon Hydroxylases, 77-6755
 DNA, Binding, 77-6755
 Polycythemia Vera
 Erythropoiesis, 77-7199
 Skin Neoplasms
 Cholanthrene, 3-Methyl-, 77-6755
 Virus, Murine Mammary Tumor
 Cells, Cultured, 77-6942
- N*-Diazoacetyl glycine Amide**
 see Acetamide, *N*-(Carbamoylmethyl)-2-diazo-
- Dibenz(a,h)anthracene**
 Cell Transformation, Neoplastic
 Histological Study, Hamster, 77-6793
 Smoking
 Carcinogen, Chemical, 77-6626
- Dibenz(a,j)acridine**
 Smoking
 Carcinogen, Chemical, 77-6626
- 1,2,3,4-Dibenzanthracene**
 see Benzo(b)triphenylene
- Dibenzo(b,def)chrysene**
 Smoking
 Carcinogen, Chemical, 77-6626
- Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-**
 Cholanthrene, 3-Methyl-
 Aryl Hydrocarbon Hydroxylases, 77-6754
 Glucosyltransferases, 77-6754
 Liver Neoplasms
 Cholangioma, 77-6814
 Lung Neoplasms
 Carcinoma, Epidermoid, 77-6814
 Microsomes, Liver
 Cytochrome P-450, 77-6813
 Neoplasms
 Rat, 77-6814
- 3-Dibenzofuranamine**
 Bladder
 Metabolism, Dog, 77-6839
- Dibutyl Cyclic AMP**
 Breast Neoplasms
 Theophylline, 77-6865
 Phosphodiesterases
 Cell Cycle Kinetics, 77-6750
 Teratoid Tumor
 Plasminogen, 77-7147
- Dichromic Acid, Dipotassium Salt**
 Fibroblasts
 Chromosome Aberrations, 77-6803
 Mitosis, 77-6803
- Dichromic Acid, Disodium Salt**
 Chromosome Aberrations
 Occupational Hazard, 77-6803
 Lymphocytes
 Chromosome Aberrations, 77-6803
- Dienestrol**
 Nervous System Neoplasms
 Urea, Methyl Nitroso-, 77-6780
 Neurofibroma
 Urea, Methyl Nitroso-, 77-6780
- Diet**
 Acetic Acid, Lead Salt
 Hematopoietic System, 77-6811
 Toxicity, Rat, 77-6811
 Arsanilic Acid
 Hematopoietic System, 77-6811
 Toxicity, Rat, 77-6811
 Biogenic Amines
 Nitrosamines, Review, 77-6611
 Breast Neoplasms
 Epidemiology, 77-7162
 Estradiol, 77-7162
 Hormones, 77-7162
 Prolactin, 77-7162
 Testosterone, 77-7162
 Cadmium Chloride
 Hematopoietic System, 77-6811
 Toxicity, Rat, 77-6811
 Colonic Neoplasms
 Epidemiology, 77-7164
 Mammary Neoplasms, Experimental
 Benz(a)anthracene, 7,12-Dimethyl-, 77-7162
 Neoplasms
 Epidemiology, Japan, 77-7163
 Nitric Acid
 Nitrosamines, Review, 77-6611
 Nitroso Compounds
 Metabolism, Review, 77-6611
 Nitrous Acid
 Nitrosamines, Review, 77-6611
- Dietary Fats**
 Colonic Neoplasms
 Adenoma, 77-6797
 Carcinoma, 77-6797
 Hydrazine, 1,2-Dimethyl-, 77-6797
 Methanol, (Methyl-*ONN*-azoxy)-, Acetate, 77-6797
 Urea, Methyl Nitroso-, 77-6797
- Dietary Proteins**
 Cyclohexane, 1,2,3,4,5,6-Hexachloro-, α -Isomer
 Liver, Rat, 77-6818
- Diethylamine, 2,2'-Dichloro-*N*-methyl-**
 DNA Replication
 Intestine, Rat, 77-6863
Salmonella typhimurium
 Mutagenic Activity, 77-6795
- Diethylamine, 1,1'-Dimethyl-*N*-nitroso-**
 Isopropyl Alcohol
 Microsomes, Liver, 77-6777
 Microsomes, Liver
 Metabolism, Rat, 77-6777

Diethylamine, 1,1'-Dimethyl-*N*-nitroso- (cont'd)

- Propyl Alcohol
 - Microsomes, Liver, 77-6777
- Diethylamine, *N*-Nitroso-**
 - Cells, Cultured
 - Mutagenic Activity, 77-6770
 - Digestive System Neoplasms
 - Transplacental Carcinogenesis, 77-6776
 - DNA
 - Disulfide, Bis(diethylthiocarbamoyl)-, 77-6767
 - Hepatoma
 - Amino Acids, 77-6765
 - Dietary Fats, 77-6765
 - Methionine, 77-6765
 - Nicotinic Acids, 77-6765
 - Kidney Neoplasms
 - Hepatectomy, 77-6769
 - Histological Study, Rat, 77-6769
 - Nicotinamide, 77-6768
 - Liver
 - Carcinogenic Activity, 77-6766
 - Mitotic Index, 77-6766
 - Liver Neoplasms
 - Carcinoma, 77-6801
 - DNA, 77-6801
 - Hemangioendothelioma, 77-6801
 - Hepatectomy, 77-6769
 - Histological Study, Rat, 77-6769
 - Models, Biological, 77-6658
 - Rat, 77-6612
 - Maternal-Fetal Exchange
 - Hamster, 77-6776
 - Mouth Neoplasms
 - Hamster, 77-6794
 - Neoplasms, Experimental
 - Fusarium*, 77-6768
 - Mycotoxins, 77-6768
 - Respiratory Tract Neoplasms
 - Review, 77-6629
 - Transplacental Carcinogenesis, 77-6776

Digestive System Neoplasms

- 1-Butanamine, *N*-Butyl-*N*-nitroso-
 - Transplacental Carcinogenesis, 77-6776
- Choline Acetate (Ester)
 - Neural Transmission, Review, 77-6653
- Diethylamine, *N*-Nitroso-
 - Transplacental Carcinogenesis, 77-6776
- Dimethylamine, *N*-Nitroso-
 - Transplacental Carcinogenesis, 77-6776
- Dipropylamine, *N*-Nitroso-
 - Transplacental Carcinogenesis, 77-6776
- Epinephrine
 - Neural Transmission, Review, 77-6653
- Norepinephrine
 - Neural Transmission, Review, 77-6653
- Piperidine, 1-Nitroso-
 - Transplacental Carcinogenesis, 77-6759

Dimethylamine

- Nitrous Acid
 - Nitrosamines, Review, 77-6611

Dimethylamine, *N*-Nitroso-

- Adrenal Glands
 - Carcinogenic Potential, Rat, 77-6769
- Barbituric Acid, 5-Ethyl-5-phenyl-
 - Mutagenic Activity, 77-6770

Dimethylamine, *N*-Nitroso- (cont'd)

- Cell Differentiation
 - Kidney, Rat, 77-6773
- Cell Transformation, Neoplastic
 - Kidney, Rat, 77-6773
- Cells, Cultured
 - Cell Differentiation, 77-6773
 - Cell Transformation, Neoplastic, 77-6773
 - Kidney, Rat, 77-6773
 - Mutagenic Activity, 77-6770, 77-6772
- Cholanthrene, 3-Methyl-
 - Mutagenic Activity, 77-6770
- Cytochrome P-450
 - Metabolism, Rat, 77-6774
- Digestive System Neoplasms
 - Transplacental Carcinogenesis, 77-6776
- Disulfide, Bis(diethylthiocarbamoyl)-
 - Metabolism, Rat, 77-6775
- DNA
 - Liver, Rat, 77-6771
- Ethyl Alcohol
 - Metabolism, Rat, 77-6775
- Formaldehyde
 - Metabolism, Rat, 77-6774
- Hematopoietic System
 - Carcinogenic Potential, Rat, 77-6769
- Hepatoma
 - Hamster, 77-6794
- Kidney Neoplasms
 - Hepatectomy, 77-6769
 - Histological Study, Rat, 77-6769
- Liver
 - Metabolism, Rat, 77-6774
- Liver Neoplasms
 - Hepatectomy, 77-6769
 - Histological Study, Rat, 77-6769
 - Models, Biological, 77-6658
 - Rat, 77-6612
 - RNA, Messenger, 77-6788
- Maternal-Fetal Exchange
 - Hamster, 77-6776
- Methanol
 - Metabolism, Rat, 77-6775
- Mitochondria
 - Oxidative Phosphorylation, 77-6800
- Mouth Neoplasms
 - Hamster, 77-6794
- Nitric Acid
 - Metabolism, 77-6715
- Nitrous Acid
 - Metabolism, 77-6715
- Oxidoreductases
 - Enzymatic Activity, 77-6774
- Purine, 2-Amino-6-methoxy-
 - Dose-Response Study, Rat, 77-6771
 - Liver, Rat, 77-6771
- Pyrazole
 - Hepatotoxicity, Rat, 77-6775
 - Metabolism, Rat, 77-6775
- Pyrazole, 4-Methyl-
 - Metabolism, Rat, 77-6775
- 1-Pyrenamine
 - Metabolism, Rat, 77-6775
- Respiratory Tract Neoplasms
 - Review, 77-6629
 - Transplacental Carcinogenesis, 77-6776
- RNA, Messenger

Dimethylamine, *N*-Nitroso- (cont'd)

- Metabolism, 77-6788
- Thymus Neoplasms
 - Carcinogenic Potential, Rat, 77-6769
- s*-Triazole, 3-Amino
 - Hepatotoxicity, Rat, 77-6775
 - Metabolism, Rat, 77-6775
- Vitamin E
 - Gastric Juice, 77-6717

Dipentylamine, *N*-Nitroso-

- Cells, Cultured
 - Mutagenic Activity, 77-6770

Diphenylamine, *N*-Nitroso-

- Cell Transformation, Neoplastic
 - Cells, Cultured, 77-6760
- Microsomes, Liver
 - Carcinogenic Activity, 77-6760

Dipropylamine, 2,2'-Diacetoxy-*N*-nitroso-

- Lip Neoplasms
 - Hamster, 77-6762
 - Histological Study, 77-6762
- Liver Neoplasms
 - Hamster, 77-6762
- Lung Neoplasms
 - Hamster, 77-6762
- Mouth Neoplasms
 - Hamster, 77-6762
 - Papilloma, 77-6762
- Pancreatic Neoplasms
 - Hamster, 77-6762
- Skin Neoplasms
 - Hamster, 77-6762
- Vaginal Neoplasms
 - Hamster, 77-6762
 - Papilloma, 77-6762
- Dipropylamine, *N*-Nitroso-
 - Cells, Cultured
 - Mutagenic Activity, 77-6770
 - Digestive System Neoplasms
 - Transplacental Carcinogenesis, 77-6776
 - Maternal-Fetal Exchange
 - Hamster, 77-6776
 - Respiratory Tract Neoplasms
 - Transplacental Carcinogenesis, 77-6776

Disgerminoma

- FSH
 - Gonadotropins, Pituitary, 77-6806
- Testicular Neoplasms
 - Copper Sulfate Pentahydrate, 77-6806
 - Epidemiology, 77-7161

Disulfide, Bis(diethylthiocarbamoyl)-

- Diethylamine, *N*-Nitroso-
 - DNA, 77-6767
- Dimethylamine, *N*-Nitroso-
 - Metabolism, Rat, 77-6775

Disulfiram

- see* Disulfide, Bis(diethylthiocarbamoyl)

Dithiothreitol

- see* 2,3-Butanediol, 1,4-Dimercapto-

DNA

- Acetamide, *N*-Fluoren-2-yl-
 - Carcinogenic Activity, 77-6835
- Acetic Acid, (*N*-Acetyl-*N*-(2-phenanthryl)amino) Ester

DNA (cont'd)

- Binding, 77-6815
- Aflatoxin B1
 - Binding, 77-6614
- Benzo(a)pyrene
 - Binding, 77-6727, 77-6735
 - Metabolism, 77-6726
 - Nucleosides, Embryo, Mouse, 77-6723
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-
 - Binding, 77-6725
- Benzo(a)pyrene-1,6-dione
 - Metabolism, 77-6726
- Benzo(a)pyrene-3,6-dione
 - Metabolism, 77-6726
- Benzo(a)pyrene-6,12-dione
 - Metabolism, 77-6726
- Butyric Acid, 2-Amino-4-(ethylthio)-
 - Liver, Rat, 77-6790
 - Methylation, 77-6790
- Chloramphenicol
 - Escherichia coli*, 77-6829
 - L(+) and D(-) Isomers, 77-6829
 - Salmonella typhimurium*, 77-6829
- Diethylamine, *N*-Nitroso-
 - Disulfide, Bis(diethylthiocarbamoyl)-, 77-6767
- Dimethylamine, *N*-Nitroso-
 - Liver, Rat, 77-6771
- Endonucleases
 - Apurinic Sites, 77-6675
- Ethanol, 2-Chloro-
 - Alkylation, 77-6824
- Ethylene, Chloro-
 - Alkylation, 77-6824
 - Liver, Mouse, 77-6824
- Liver Neoplasms
 - Acetamide, *N*-Fluoren-2-yl-, 77-6801
 - Aflatoxin B1, 77-6801
 - Diethylamine, *N*-Nitroso-, 77-6801
- Proteins
 - Alkylation, 77-6824
- Radiation, Ionizing
 - DNA Repair, 77-6675
- Virus, Rauscher Murine Leukemia
 - Reverse Transcriptase, 77-6954

DNA, Bacterial

- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-
 - Adduct Formation, 77-6723

DNA Nucleotidyltransferases

- Breast Neoplasms
 - Isolation and Characterization, 77-7190
- Carcinoma, Bronchogenic
 - Cytosine, 1- β -*D*-Arabinofuranosyl-, Monohydrochloride, 77-7190
 - Isolation and Characterization, 77-7190
 - Novobiocin, 77-7190
- Cecal Neoplasms
 - Isolation and Characterization, 77-7190
- Cytosine, 1- β -*D*-Arabinofuranosyl-, Monohydrochloride
 - Liver Regeneration, 77-7190
- Novobiocin
 - Liver Regeneration, 77-7190
- Radiation
 - Lymphocytes, 77-6898
- Virus, Rous Sarcoma

DNA Nucleotidyltransferases (cont'd)

RNA, Viral, 77-6924

DNA RepairAcetamide, *N*-(Carbamoylmethyl)-2-diazo-
Cells, Cultured, 77-6850Arsenious Acid, Sodium Salt
Escherichia coli, 77-6808Benzo(a)pyrene
Diol Epoxides, 77-6724
Guanosine, 2'-Deoxy-, 77-6724*Escherichia coli*
Antipain, 77-6674
Cell Survival, 77-6904
Isolation and Characterization, 77-6906Guanidine, 1-Methyl-3-nitro-1-nitroso-
Salmonella typhimurium, 77-6749Hereditary Diseases
Ultraviolet Rays, 77-6903Neoplasms, Multiple Primary
Ultraviolet Rays, 77-6903Osmium Tetroxide
Endonucleases, 77-6906Quinoline, 4-Nitro-, 1-Oxide
Cell Transformation, Neoplastic, 77-6858
Cells, Cultured, 77-6792*Salmonella typhimurium*, 77-6749

Virus, Rauscher Murine Leukemia, 77-6858

Radiation, Ionizing

DNA, 77-6675
Endonucleases, 77-6906Sulfuric Acid, Dimethyl Ester
Cells, Cultured, 77-679212-*O*-Tetradecanoylphorbol-13-acetate
Salmonella typhimurium, 77-6749

Ultraviolet Rays

Aflatoxin B1, 77-6667
Arsenious Acid, Sodium Salt, 77-6808

Cell Survival, 77-6904

Culture Media, 77-6904

Endonucleases, 77-6906

Escherichia coli, 77-6904

Virus, Rauscher Murine Leukemia, 77-6858

Urea, Ethyl Nitroso-

Cells, Cultured, 77-6792

Urea, Hydroxy-

Cell Cycle Kinetics, 77-6787

Urea, Methyl Nitroso-

Cells, Cultured, 77-6792

Virus, Herpes Simplex 1

Ultraviolet Rays, 77-7002

Xeroderma Pigmentosum

Caffeine, 77-6903

Cells, Cultured, 77-6792

Complementation Group, 77-6903

Ultraviolet Rays, 77-6903

DNA ReplicationAcetamide, *N*-Fluoren-2-yl-
Barbituric Acid, 5-Ethyl-5-phenyl-, 77-6837Aflatoxin B1
Cells, Cultured, 77-6667

Breast Neoplasms

Insulin, 77-6865

Theophylline, 77-6865

Cholanthrene, 3-Methyl-

Cell Transformation, Neoplastic, 77-6680

Lymph Nodes, 77-6680

DNA Replication (cont'd)

Lymphocytes, 77-6680

Cyclohexane, 1,2,3,4,5,6-Hexachloro-, α -Isomer

Cell Cycle Kinetics, 77-6818

Liver, Rat, 77-6818

Diethylamine, 2,2'-Dichloro-*N*-methyl-

Intestine, Rat, 77-6863

Erythroleukemia

Methane, Sulfinylbis-, 77-7179

Leukemia, Lymphocytic

Lymphocyte Culture Test, Mixed, 77-7073

T-Lymphocytes, 77-7073

Methanol, (Methyl-*ONN*-azoxy)-

Intestine, Rat, 77-6863

Quinoline, 4-Nitro-, 1-Oxide

Cells, Cultured, 77-6861

Species Difference, 77-6861

Radiation

Lymphocytes, 77-6898

Reverse Transcriptase

Isolation and Characterization, 77-6951

Sarcoma

Cell Membrane, 77-7189

Cytosine Nucleotides, 77-7189

Deoxyribonuclease, 77-7189

Guanosine Triphosphate, 77-7189

1*H*-Pyrrole-2,5-dione, 1-Ethyl-, 77-7189

Uracil Nucleotides, 77-7189

Virus, Rous Sarcoma, 77-7189

12-*O*-Tetradecanoylphorbol-13-acetate

Cell Transformation, Neoplastic, 77-6744

Embryo, Hamster, 77-6744

Ultraviolet Rays

Aflatoxin B1, 77-6667

Uracil, 5-Fluoro-

Intestine, Rat, 77-6863

Urea, Hydroxy-

Deoxyribonucleosides, 77-6787

L Cells, 77-6787

Virus, Adeno 1

Virus, Adeno 5, 77-6986

Virus, Helper, 77-6986

Virus, Avian Leukosis

Reverse Transcriptase, 77-6916

Virus, Avian Sarcoma

Reverse Transcriptase, 77-6916

Virus, Rauscher Murine Leukemia

Reverse Transcriptase, 77-6951

Virus, Rous Sarcoma

RNA, Viral, 77-6924

Virus, SV40

Cell Cycle Kinetics, 77-7022

Cell Transformation, Neoplastic, 77-7022

Cycloheximide, 77-7022

DNA, Viral, 77-7018

Hybrid Cells, 77-7010

DNA, Viral

Ultraviolet Rays

Haemophilus influenzae, 77-6907

Thymine Photoproduct, 77-6907

Virus, Adeno 1

Replication Complex, Isolation and Characteriza-
tion, 77-6986

Virus, Adeno 12

Cell Transformation, Neoplastic, 77-6988

DNA-DNA Hybridization, 77-6988

Isolation and Characterization, 77-6988

DNA, Viral (cont'd)

- Reassociation Kinetics, 77-6988
- Virus, Avian Leukosis-Sarcoma
 - Binding Sites, 77-6923
 - Endonucleases, 77-6923
- Virus, Avian Reticuloendotheliosis
 - Cytopathogenic Effect, Viral, 77-6923
 - Endonucleases, 77-6923
- Virus, Avian Sarcoma
 - Cell Transformation, Neoplastic, 77-6921
 - DNA-RNA Hybridization, 77-6919
- Virus, Herpes Simplex 1
 - Urea, Hydroxy-, 77-7001
- Virus, Moloney Murine Sarcoma
 - DNA-RNA Hybridization, 77-6968
 - Endonucleases, 77-6968
 - Isolation and Characterization, 77-6968
 - Virus Replication, 77-6968
- Virus, Murine Mammary Tumor
 - Hepatosarcoma, 77-6941
- Virus, Polyoma
 - DNA-RNA Hybridization, 77-6977
 - Temperature Sensitive Mutants, 77-6977
- Virus, Polyoma, BK
 - Cell Transformation, Neoplastic, 77-6982
 - Isolation and Characterization, 77-6982
- Virus, SV40
 - Base Sequence, 77-7017
 - Chromatin, 77-7028
 - Chromosomes, 77-7029, 77-7139
 - DNA Replication, 77-7018
 - DNA-RNA Hybridization, 77-7018
 - Hairpin Turns, 77-7025
 - Isolation and Characterization, 77-7014
 - Nucleic Acid Denaturation, 77-7025
 - Psoralen, 4,5',8-Trimethyl-, 77-7025
 - Temperature Sensitive Mutants, 77-7020, 77-7021
 - Ultrastructural Study, 77-7025
 - Virus, Recombinant, 77-7020, 77-7021

Drug Therapy

- Leukemia
 - Lymphoma, 77-6659
- Lung Neoplasms
 - Carcinoma, 77-6895

Endonucleases

- DNA
 - Apurinic Sites, 77-6675
- Escherichia coli*
 - Isolation and Characterization, 77-6675
- Osmium Tetroxide
 - DNA Repair, 77-6906
- Radiation, Ionizing
 - DNA Repair, 77-6906
- Ultraviolet Rays
 - DNA Repair, 77-6906
- Virus, Avian Leukosis-Sarcoma
 - Binding Sites, 77-6923
 - DNA, Viral, 77-6923
- Virus, Avian Reticuloendotheliosis
 - Binding Sites, 77-6923
 - Cytopathogenic Effect, Viral, 77-6923
 - DNA, Viral, 77-6923
- Virus, Moloney Murine Sarcoma
 - DNA, Viral, 77-6968
- Virus, SV40
 - Virus, Recombinant, 77-7021

Endoplasmic Reticulum

- Fibrosarcoma
 - Virus-Like Particles, 77-7012

Environmental Hazard

- Benzidine
 - Food-Chain Transfer, 77-6796
- Benzo(a)pyrene
 - Food-Chain Transfer, 77-6796
- Carcinogen, Chemical
 - Dose-Response Study, 77-6896
- Ethylene, Chloro-
 - Food-Chain Transfer, 77-6796
- Radiation, Ionizing
 - Dose-Response Study, 77-6896

Enzymes

- Lung
 - Isolation and Characterization, 77-7195
- Lung Neoplasms
 - Isolation and Characterization, 77-7195

Ependymoma

- Nervous System Neoplasms
 - Urea, 1-Butyl-1-nitroso-, 77-6778

Epinephrine

- Aging
 - Neural Transmission, Review, 77-6653
- Digestive System Neoplasms
 - Neural Transmission, Review, 77-6653
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Adenosine Cyclic 3',5' Monophosphate, 77-6747

Epoxide Hydratases

- Barbituric Acid, 5-Ethyl-5-phenyl-
 - Enzymatic Activity, 77-6753
- Benzene, (Epoxymethyl)-
 - Enzymatic Activity, 77-6753
- Cholanthrene, 3-Methyl-
 - Enzymatic Activity, 77-6753
- Lung
 - Rat, 77-6753

Erythrocytes

- Leukemia, Myelocytic
 - Isolation and Characterization, 77-7077
- Spherocytosis, Hereditary
 - Phosphorylation, 77-7185

Erythroleukemia

- Acetamide, *N,N*-Dimethyl-
 - Cell Differentiation, 77-7179
- Butyric Acid
 - Cell Differentiation, 77-7179
- Cells, Cultured
 - Carbonic Anhydrase, 77-7187
- Methane, Sulfinylbis-
 - Cell Cycle Kinetics, 77-7179
 - Cell Differentiation, 77-7179
 - Chromatin, 77-7179
 - DNA Replication, 77-7179
- Virus, Friend Murine Leukemia
 - Reverse Transcriptase, 77-6956

Erythropoiesis

- Agammaglobulinemia
 - Lymphocytes, 77-7064
- Polycythemia Vera
 - Bone Marrow Cells, 77-7199
 - Dexamethasone, 77-7199

Erythropoiesis (cont'd)

- Erythropoietin, 77-7199
- Virus, Friend Murine Leukemia
- Cell Transformation, Neoplastic, 77-6956
- Reverse Transcriptase, 77-6956
- Water, Heavy
- Bone Marrow Cells, 77-7138

Erythropoietin

- Polycythemia Vera
- Erythropoiesis, 77-7199
- Virus, Meningitis
- Hematopoietic Stem Cells, 77-6944

Escherichia coli

- Arsenious Acid, Sodium Salt
- DNA Repair, 77-6808
- Galactosidases, 77-6808
- RNA Replication, 77-6808
- Chloramphenicol
- DNA, 77-6829
- Mutagenic Activity, 77-6829
- DNA Repair
- Antipain, 77-6674
- Cell Survival, 77-6904
- Isolation and Characterization, 77-6906
- Endonucleases
- Isolation and Characterization, 77-6675
- Ultraviolet Rays
- DNA Repair, 77-6904

Esophageal Neoplasms

- Neoplasms, Multiple Primary
- Precancerous Conditions, 77-7104
- Riboflavine
- Carcinogen, Chemical, 77-6666
- Stomach Neoplasms
- Neoplasms, Multiple Primary, 77-7104

Erasers

- Leukemia, Hairy Cell
- Monocytes, 77-7075

Estradiol

- Animal Feed
- Toxicology, 77-6868
- Breast Neoplasms
- Body Fluids, Review, 77-6618
- Diet, 77-7162
- Epidemiology, Review, 77-6618
- Insulin, 77-6865
- Prolactin, 77-6865
- Hepatoma
- Metabolism, 77-7200
- Mammary Neoplasms, Experimental
- Acetamide, *N*-Fluorenyl-, 77-6834
- Estradiol, Ethinyl-11 α -methoxy-, 77-6695, 77-6696
- Inhibitory Effects, Review, 77-6618
- Neonate, Mouse, 77-6875
- Progesterone, 77-6875
- Progesterone
- Co-carcinogenic Activity, Mouse, 77-6875
- Receptors, Hormone
- Mammary Neoplasms, Experimental, 77-6692
- Uterine Neoplasms
- Adenocarcinoma, 77-6867
- Histological Study, 77-6867
- Ultrastructural Study, 77-7116
- Vaginal Neoplasms
- Hyperplasia, 77-6875

Estradiol (cont'd)

- Neonate, Mouse, 77-6875
- Progesterone, 77-6875

Estradiol, Ethinyl-11 α -methoxy-

- Mammary Neoplasms, Experimental
- Benz(a)anthracene, 7,12-Dimethyl-, 77-6695
- 77-6696
- Estradiol, 77-6695, 77-6696
- Insulin, 77-6695
- Progesterone, 77-6695
- Prolactin, 77-6695, 77-6696
- Receptors, Hormone, 77-6695, 77-6696
- Somatotropin, 77-6695

Estradiol, 17-Ethinyl-

- Liver Neoplasms
- Adenoma, 77-7110
- Precancerous Conditions, 77-7159

Estriol

- Hepatoma
- Metabolism, 77-7200

Estrogenic Substances, Conjugated

- Breast Neoplasms
- Epidemiology, 77-6873
- Cervix Neoplasms
- Case Report, 77-7115
- Histological Study, 77-7115
- Uterine Neoplasms
- Carcinoma, 77-6874
- Epidemiology, 77-6874

Estrogens

- Breast Neoplasms
- Epidemiology, Review, 77-6620
- Neoplasms, Multiple Primary
- Receptors, Hormone, Review, 77-6617
- Uterine Neoplasms
- Epidemiology, 77-6616

Estrone

- Prostatic Neoplasms
- Adenocarcinoma, 77-6876

Estrus

- Mammary Neoplasms, Experimental
- Leucine, 77-6702
- Thymidine, 77-6702

Ethacrynic Acid

- see Acetic Acid, (2,3-Dichloro-4-(2-methylenebutyryl)phenoxy)-

Ethane, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)-

- Actinomycin D
- Liver, Rat, 77-6822
- α -Amanitine
- Actinomycin D, 77-6822
- Cytochrome P-450
- Liver, Rat, 77-6822
- Proteins
- Liver, Rat, 77-6822

Ethane, 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)-

- Adrenal Gland Diseases
- Benz(a)anthracene, 7,12-Dimethyl-, 77-6821
- Enzyme Induction
- Liver, Rat, 77-6821

Ethanol, 2,2-Bis(*p*-chlorophenyl)-

- Adrenal Gland Diseases

- Ethanol, 2,2-Bis(*p*-chlorophenyl)- (cont'd)**
Benz(a)anthracene, 7,12-Dimethyl-, 77-6821
- Ethanol, 2-Chloro-**
DNA
Alkylation, 77-6824
- Ether, Bis(chloromethyl)-**
Cell Transformation, Neoplastic
Animal Model, Review, 77-6601
- Ethidium Bromide**
Salmonella typhimurium
Mutagenic Activity, 77-6828
- Ethionine**
see Butyric Acid, 2-Amino-4-(ethylthio)-
- Ethyl Alcohol**
Chromosome Aberrations
Leukocytes, Review, 77-6610
Dimethylamine, *N*-Nitroso-
Metabolism, Rat, 77-6775
Epidemiology
Statistical Analysis, 77-7148
Neoplasm Metastasis
Epidemiology, 77-7148
Oxidoreductases
Intestines, Rat, 77-6862
Liver, Rat, 77-6862
Ozone
Mutagenic Activity, 77-6798
RNA Replication
HeLa Cells, Review, 77-6610
Water Pollutants
Ozone, 77-6798
- Ethylene, 1,1-Bis(*p*-chlorophenyl)-2-chloro-**
Adrenal Glands
Benz(a)anthracene, 7,12-Dimethyl-, 77-6821
- Ethylene, Chloro-**
Angiosarcoma
Epidemiology, Review, 77-6623
Cell Transformation, Neoplastic
Animal Model, Review, 77-6601
Cells, Cultured, 77-6760
Chromosome Aberrations
Epidemiology, 77-6827
DNA
Alkylation, 77-6824
Liver, Mouse, 77-6824
Environmental Hazard
Food-Chain Transfer, 77-6796
Ethylene Oxide, Chloro-
Carcinogenic Metabolite, 77-6824
Germ Cells
Mutagenic Activity, Review, 77-6625
Hemoglobins
Alkylation, 77-6824
Liver Diseases
Occupational Hazard, Review, 77-6623
Liver Neoplasms
Angiosarcoma, 77-6624, 77-6825
Carcinoma, 77-6825
Occupational Hazard, 77-6622, 77-6825
Occupational Hazard, Review, 77-6623
Lung Neoplasms
Adenoma, 77-6624
Mammary Neoplasms, Experimental
Carcinoma, 77-6624
- Ethylene, Chloro- (cont'd)**
Metabolism
Rat, 77-6826
Microsomes, Liver
Carcinogenic Activity, 77-6760
Mutagenic Activity
Correlation, Carcinogenic Activity, Review, 77-6607
Occupational Hazard
Epidemiology, 77-6825
Piperonyl Butoxide
Metabolism, Aquatic Organisms, 77-6796
Proteins
Testis, Mouse, 77-6824
Soil
Degradation, 77-6796
- Ethylene, Chloro- Polymer**
Foreign Body Reaction
Acetic Acid, Vinyl Ester, 77-6910
Sarcoma
Acetic Acid, Vinyl Ester, 77-6910
Antilymphocyte Serum, 77-7035
Azathioprine, 77-7035
Histocompatibility Antigens, 77-7035
Immunosuppression, 77-7035
- Ethylene, 1,1-Dichloro-**
Cell Transformation, Neoplastic
Animal Model, Review, 77-6601
Food Additives
Cell Transformation, Neoplastic, 77-6601
- Ethylene, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)-**
Adrenal Gland Diseases
Benz(a)anthracene, 7,12-Dimethyl-, 77-6821
Enzyme Induction
Liver, Rat, 77-6821
- Ethylene Oxide, Chloro-**
Ethylene, Chloro-
Carcinogenic Metabolite, 77-6824
- Fetal Globulins**
Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
Liver Neoplasms, 77-6848
Carbon Tetrachloride
Blood Proteins, 77-6823
Liver Neoplasms
Acetamide, *N*-Fluoren-2-yl-, 77-7109
Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-, 77-7109
Carcinoma, 77-7160
- Fiber Glass**
Particle Size
Carcinogenic Potential, 77-6911
Pleural Neoplasms
Particle Size, 77-6911
Sarcoma, 77-6911
- Fibrin**
Cells, Cultured
Cell Adhesion, 77-7183
Fibrinolysis, 77-7183
Hexanoic Acid, 6-Amino-
Cell Adhesion, 77-7183
Surface Properties
Ovary, Hamster, 77-7183
- Fibrinogen**
Cycloheximide

Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)- (cont'd)

Dose-Response Study, Mouse, 77-7033

Bladder Neoplasms

Histological Study, 77-6841

Rat, 77-6841

Ultrastructural Study, 77-6841

Ultrastructural Study, Rat, Review, 77-6657

Salmonella typhimurium

Mutagenic Activity, 77-6840

2-Formylamine-4-(5-nitro-2-furyl)-thiazol

see Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-

FSH

Disgerminoma

Gonadotropins, Pituitary, 77-6806

Leydig Cell Tumor

Gonadotropins, Pituitary, 77-6806

LH

Gonadotropins, Pituitary, 77-6806

Teratoid Tumor

Gonadotropins, Pituitary, 77-6806

Fucose

Cell Transformation, Neoplastic

Glycopeptides, 77-6971

Furan, 2-Methyl-5-nitro-

Cells, Cultured

Cell Transformation, Neoplastic, 77-6842

Fibrosarcoma

Hamster, 77-6842

Fusarium

Neoplasms, Experimental

Diethylamine, *N*-Nitroso-, 77-6768

Galactosidases

Arsenious Acid, Sodium Salt

Escherichia coli, 77-6808

Asbestos

Lung, 77-6912

Galactosyltransferases

Cell Transformation, Neoplastic

Animal Model, Hamster, 77-6980

Neoplasms, Experimental

Isolation and Characterization, Serum, 77-6980

Virus, Polyoma, 77-6980

Gastric Juice

Dimethylamine, *N*-Nitroso-

Vitamin E, 77-6717

Nitrous Acid, Sodium Salt

Ascorbic Acid, 77-6717

Vitamin E, 77-6717

Gastrointestinal System

Nitric Acid

Metabolism, 77-6716

Nitrous Acid

Metabolism, 77-6716

Rat, 77-6716

Genetics

Aryl Hydrocarbon Hydroxylases

Models, Theoretical, 77-6752

Monocytes, 77-6756

Mouse, 77-6752

Ataxia Telangiectasia

Virus, Epstein-Barr, 77-6991

Benz(a)anthracene

Genetics (cont'd)

Aryl Hydrocarbon Hydroxylases, 77-6756

Breast Neoplasms

Age Factors, 77-7113

Epidemiology, 77-7113

Neoplasms, Multiple Primary, 77-7113

Precancerous Conditions, 77-7150

Cell Transformation, Neoplastic

Mutation, Review, 77-6660

Risk Factor, Review, 77-6660

Colonic Neoplasms

Case Report, 77-7151

Hydrazine, 1,2-Dimethyl-, 77-6855

Intestinal Neoplasms

Chromosome Abnormalities, 77-7105

Polyps, 77-7105

Lung Neoplasms

Carcinoma, Bronchiolar, 77-7096

Carcinoma, Bronchogenic, 77-7093

Polyps

Chromosome Abnormalities, 77-7105

Precancerous Conditions

Epidemiology, Review, 77-7150

Skin Neoplasms

Melanoma, 77-6636

Virus, C-Type RNA Tumor

Viral Proteins, 77-7007

Virus, Kirsten Murine Sarcoma

Colonic Neoplasms, 77-6974

Glioma

Nervous System Neoplasms

Urea, 1-Butyl-1-nitroso-, 77-6778

Urea, Ethyl Nitroso-

Chromosomes, 77-7137

Glucocorticoids

Lymphocytes

Receptors, Hormone, 77-7198

Glucosaminidase

Asbestos

Lung, 77-6912

Glucose

Calcium

Biological Transport, 77-7196

Fibroblasts

Binding Factor, 77-6927

Magnesium

Biological Transport, 77-7196

Virus, Rous Sarcoma

Binding Factor, 77-6927

Cell Transformation, Neoplastic, 77-6927

Glucose, 2-Deoxy-

Glycoproteins

Cells, Cultured, 77-7181

Toxicology

Cells, Cultured, 77-7181

Virus, Rous Sarcoma

Cartilage, 77-6929

Glucosephosphate Dehydrogenase

Smoking

Histochemical Study, Vero Cells, 77-6700

Glucosyltransferases

Cholanthrene, 3-Methyl-

Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-, 77-6754

Liver, Mouse, 77-6754

Glucosyltransferases (cont'd)

Strain Difference, Mouse, 77-6754

Glucuronidase

Asbestos
Lung, 77-6917

Glutaraldehyde

Leukemia L1210
Immune Response, 77-7040

Glutathione

Streptozotocin
Maleic Acid, 77-6779
Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
Guanyl Cyclase, 77-6779

Glycogen Phosphorylase

Morpholine, *N*-Nitroso-
Liver, Rat, 77-6709

Glycogenesis

Hepatoma
Morpholine, *N*-Nitroso-, 77-6708
Morpholine, *N*-Nitroso-
Cell Transformation, Neoplastic, 77-6709
Liver, Rat, 77-6709

Glycolipids

Virus, Kirsten Murine Sarcoma
Cell Transformation, Neoplastic, 77-7057

Glycopeptides

Cell Transformation, Neoplastic
Cell Membrane, 77-6971
Epithelial Cells, 77-6971
Fucose, 77-6971
Epithelial Cells
Temperature Sensitive Mutants, 77-6971
Hepatoma
Cell Membrane, 77-6971

Glycoproteins

Bronchi
Organ Culture, 77-7092
Smoking, 77-7092
Glucose, 2-Deoxy-
Cells, Cultured, 77-7181
B-Lymphocytes
Isolation and Characterization, 77-7079
Virus, Avian Leukosis-Sarcoma
Antigenic Determinants, 77-6919
Virus, Avian Sarcoma
Deletion Mutant, 77-6919
Virus, Friend Murine Leukemia
Antibody Specificity, 77-6960
Antigen-Antibody Reactions, 77-6960
Immune Response, 77-6960
Virus, Murine Leukemia
Virus, Recombinant, 77-6965

Goiter, Exophthalmic

Thyroid Neoplasms
Carcinoma, 77-6633
Radiotherapy, 77-6632

Gonadoblastoma

see Disgerminoma

Gonadotropins, Pituitary

Disgerminoma

Gonadotropins, Pituitary (cont'd)

FSH, 77-6806

FSH

LH, 77-6806

Leydig Cell Tumor

FSH, 77-6806

LH, 77-6806

Teratoid Tumor

FSH, 77-6806

LH, 77-6806

Testicular Neoplasms

Copper Sulfate Pentahydrate, 77-6806

Graft vs Host Reaction

Acetamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
Dose-Response Study, Mouse, 77-7033

Lymphoid Tissue

Transplacental Carcinogenesis, 77-7038

Pregnancy

Transplacental Carcinogenesis, 77-7038

Virus, Marek's Disease

Histocompatibility Antigens, 77-7089

Isoantigens, 77-7089

Graft Rejection

Benzo(a)pyrene

Immunity, Cellular, 77-7048

Carcinoma, Epidermoid

Antigenic Determinants, 77-7083

Mammary Neoplasms, Experimental

Immunity, Passive, 77-7034

Immunosuppression, 77-7034

Radiation, Ionizing, 77-7034

Vascular Reactions, 77-7034

Granular Cell Tumor, Malignant

see Sarcoma

Granuloma

Histiocytes

Case Report, 77-7102

Diagnosis and Prognosis, 77-7102

Graves' Disease

see Goiter, Exophthalmic

Growth

Carcinoma

Immunoglobulins, Surface, 77-7063

Neoplasms, Experimental

Ascorbic Acid, 77-6679

Sarcoma, Mast Cell

Antigens, Neoplasm, 77-7049

Immunoglobulins, Surface, 77-7049

Guanidine, Dodecyl-, Acetate

Lung Neoplasms

Adenocarcinoma, 77-6786

Transplacental Carcinogenesis, 77-6786

Lymphoma

Transplacental Carcinogenesis, 77-6786

Lymphosarcoma

Transplacental Carcinogenesis, 77-6786

Nitrous Acid, Sodium Salt

Nitroso Compounds, 77-6786

Rectal Neoplasms

Adenocarcinoma, 77-6786

Transplacental Carcinogenesis, 77-6786

Urea, Dodecyl Nitroso-

Isolation and Characterization, 77-6786

- Guanidine, 1-Ethyl-3-nitro-1-nitroso-**
 Stomach Neoplasms
 Adenocarcinoma, 77-6710, 77-6711
 Carcinoma, Epidermoid, 77-6710
 Histological Study, Rat, 77-6711
 Neoplasm Metastasis, 77-6711
 Precancerous Conditions, 77-6711
 Ultrastructural Study, Rat, 77-6710
- Guanidine, Methyl-**
 Angiosarcoma
 Nitrous Acid, Sodium Salt, 77-6714
 Bile Duct Neoplasms
 Adenoma, 77-6714
 Nitrous Acid, Sodium Salt, 77-6714
 Hemangioma
 Nitrous Acid, Sodium Salt, 77-6714
 Hepatoma
 Nitrous Acid, Sodium Salt, 77-6714
 Liver Neoplasms
 Hemangioma, 77-6714
 Nitrous Acid, Sodium Salt, 77-6714
 Sarcoma
 Nitrous Acid, Sodium Salt, 77-6714
- Guanidine, 1-Methyl-3-nitro-1-nitroso-**
 Cell Transformation, Neoplastic
 Histological Study, Hamster, 77-6793
 Strain Difference, Mouse, 77-7144
 Colonic Neoplasms
 Adenocarcinoma, 77-6712
 Adenoma, 77-6712
 Bile Acids and Salts, 77-6712
 Contact Inhibition
 Cell Transformation, Neoplastic, 77-7144
 Guanosine Cyclic 3',5' Monophosphate
 Liver, Renal Cortex, Dog, 77-6779
 Guanyl Cyclase
 Cations, Divalent, 77-6779
Salmonella typhimurium
 DNA Repair, 77-6749
 Mutagenic Activity, 77-6749, 77-6795
 Stomach Neoplasms
 Adenocarcinoma, 77-6710, 77-6711
 Adenoma, 77-6713
 Carcinoma, 77-6713
 Carcinoma, Epidermoid, 77-6710
 Histological Study, Rat, 77-6711
 Lysosomes, 77-6713
 Neoplasm Metastasis, 77-6711
 Precancerous Conditions, 77-6711, 77-6713
 Ultrastructural Study, Rat, 77-6710, 77-6713
 Teratoid Tumor
 Cell Differentiation, 77-7044
 Immunity, Passive, 77-7044
 Transplantation Immunology, 77-7044
- Guanine Nucleotides**
 Acridine, 9-Amino-
 Complex, Crystalline, 77-6851
 DNA, Binding, 77-6851
 Mutagenic Activity, 77-6851
- Guanosine Cyclic 3',5' Monophosphate**
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 Liver, Renal Cortex, Dog, 77-6779
 Hepatoma
 Cells, Cultured, 77-7193
 Streptozotocin
- Guanosine Cyclic 3',5' Monophosphate (cont'd)**
 Liver, Renal Cortex, Dog, 77-6779
 Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
 Liver, Renal Cortex, Dog, 77-6779
 Urea, Methyl Nitroso-
 Liver, Renal Cortex, Dog, 77-6779
- Guanosine, 2'-Deoxy-**
 Benzo(a)pyrene
 Adduct Formation, 77-6724
 DNA Repair, 77-6724
 Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-
 tetrahydro-
 Binding, 77-6725
- Guanosine Triphosphate**
 Sarcoma
 DNA Replication, 77-7189
- Guanyl Cyclase**
 Guanidine, 1-Methyl-3-nitro-1-nitroso-
 Cations, Divalent, 77-6779
 Streptozotocin
 2,3-Butanediol, 1,4-Dimercapto-, 77-6779
 Cations, Divalent, 77-6779
 Enzyme Activation, Rat, 77-6781
 Kidney, 77-6779
 Maleic Acid, 77-6779
 1*H*-Pyrrole-2,5-dione, 1-Ethyl-, 77-6779
 Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
 2,3-Butanediol, 1,4-Dimercapto-, 77-6779
 Cations, Divalent, 77-6779
 Cysteine, 77-6779
 Glutathione, 77-6779
 Kidney, 77-6779
 Maleic Acid, 77-6779
 Maleimide, *N*-Ethyl-, 77-6779
 Urea, Methyl Nitroso
 Cations, Divalent, 77-6779
 Enzyme Activation, Rat, 77-6781
- Gynecologic Neoplasms**
 4,4'-Stilbenediol, α,α' -Diethyl-
 Age Factors, 77-7157
 Epidemiology, 77-7157
 Precancerous Conditions, 77-6870
 Precancerous Conditions, Review, 77-6615
 Transplacental Carcinogenesis, 77-6870, 77-7157
 Transplacental Carcinogenesis, Review, 77-6615
- Haemophilus influenzae***
 Ultraviolet Rays
 DNA, Viral, 77-6907
- Hamartoma**
 Liver Neoplasms
 Contraceptives, Oral, 77-6621
- Haptens**
 T-Lymphocytes
 Immunity, Passive, 77-7067
- Head and Neck Neoplasms**
 Angiosarcoma
 Case Report, 77-6894
 Radiation, Ionizing, 77-6894
 Carcinoma, Epidermoid
 Immunity, Cellular, 77-7071
 Immunity, Cellular
 Lymph Nodes, Regional, 77-7071
 Lymph Nodes

Head and Neck Neoplasms (cont'd)

- IgG, 77-7072
- Immunoglobulins, 77-7072
- T-Lymphocytes, 77-7072
- Lymphocytes
- Concanavalin A, 77-7071
- Plant Agglutinins, 77-7071

Hemangioendothelioma

- Liver Neoplasms
- Diethylamine, *N*-Nitroso-, 77-6801

Hemangioma

- Angiosarcoma
- Radiation, Ionizing, 77-6894
- Liver Neoplasms
- Guanidine, Methyl-, 77-6714
- Nitrous Acid, Sodium Salt, 77-6714
- Nitrous Acid, Sodium Salt
- Guanidine, Methyl-, 77-6714
- Skin Neoplasms
- Epidemiology, Review, 77-6656

Hemangiosarcoma

- see Angiosarcoma

Hematopoiesis

- Mammary Neoplasms, Experimental
- Kinetic Study, 77-7133

Hematopoietic Stem Cells

- Virus, Friend Murine Leukemia
- Cell Differentiation, 77-6937
- Virus, Meningitis
- Colony Formation, 77-6944
- Erythropoietin, 77-6944
- Interferon, 77-6944
- Iron, 77-6944
- Virus, Moloney Murine Leukemia
- Cell Differentiation, 77-6937
- Virus, Rauscher Murine Leukemia
- Cell Differentiation, 77-6950
- Methanesulfonic Acid, Isopropyl Ester, 77-6950

Hematopoietic System

- Acetic Acid, Lead Salt
- Diet, 77-6811
- Arsanilic Acid
- Diet, 77-6811
- Cadmium Chloride
- Diet, 77-6811
- Dimethylamine, *N*-Nitroso-
- Carcinogenic Potential, Rat, 77-6769

Hemoglobins

- Ethylene, Chloro-
- Alkylation, 77-6824
- Smoking
- Nicotine, 77-6758

Heparin

- Cell Transformation, Neoplastic
- Mouse, 77-6973
- Virus, Kirsten Murine Sarcoma
- Cell Transformation, Neoplastic, 77-6973
- Virus, SV40
- Cell Transformation, Neoplastic, 77-6973

Hepatoma

- Adenosine Cyclic 3',5' Monophosphate
- Cells, Cultured, 77-7193
- Androgens

Hepatoma (cont'd)

- Epidemiology, Review, 77-6621
- Aniline, *N,N*-Dimethyl-*p*-phenylazo-
- Immune Response, 77-6847
- Aniline, 2,4,6-Trimethyl-
- Chromosome Abnormalities, 77-6849
- Barbituric Acid, 5-Ethyl-5-phenyl-
- Hydroxylases, Estrogen, 77-7200
- Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
- Besnoitia jellisoni*, 77-7061
- Toxoplasma gondii*, 77-7061
- Brain Neoplasms
- Neoplasm Metastasis, 77-7136
- Concanavalin A
- Binding, 77-7191
- Tyrosine Aminotransferase, 77-7191
- Contraceptives, Oral
- Epidemiology, 77-7159
- Epidemiology, Review, 77-6621
- Review, 77-6622
- Diethylamine, *N*-Nitroso-
- Amino Acids, 77-6765
- Dietary Fats, 77-6765
- Methionine, 77-6765
- Nicotinic Acids, 77-6765
- Dimethylamine, *N*-Nitroso-
- Hamster, 77-6794
- Estradiol
- Metabolism, 77-7200
- Estriol
- Metabolism, 77-7200
- Glycopeptides
- Cell Membrane, 77-6971
- Guanosine Cyclic 3',5' Monophosphate
- Cells, Cultured, 77-7193
- Histological Study
- Hamster, 77-6794
- D*-Mannopyranoside, α -Methyl-
- Concanavalin A, 77-7191
- Tyrosine Aminotransferase, 77-7191
- Morpholine, *N*-Nitroso-
- Glycogenosis, 77-6708
- Precancerous Conditions, 77-6708
- Neoplasm Circulating Cells
- Sarcoma, Yoshida, 77-7136
- Transcerebral Passage, 77-7136
- Neoplasm Transplantation
- Histological Study, 77-7108
- Nitrous Acid, Sodium Salt
- Guanidine, Methyl-, 77-6714
- Steroids
- Review, 77-6622
- Streptozotocin
- Histological Study, 77-6673
- Virus, Hepatitis
- Antigen-Antibody Reactions, 77-6989
- Epidemiology, Uganda, 77-6989
- Virus, Murine Mammary Tumor
- Antigens, Viral, 77-6942
- Cells, Cultured, 77-6942
- DNA, Viral, 77-6941
- RNA, Viral, 77-6942
- Virus Replication, 77-6941, 77-6942

Herbicides

- Cell Transformation, Neoplastic
- Animal Model, Review, 77-6601

Hereditary Diseases

- Ultraviolet Rays
- DNA Repair, 77-6903

1-Hexanamine, *N*-Hexyl-

- 1-Decanaminium, *N,N,N*-Trimethyl-, Bromide
- Nitrosation Kinetics, 77-6763
- Lecithins
- Nitrous Acid, 77-6763
- Nitrous Acid
- 1-Decanaminium, *N,N,N*-Trimethyl-, Bromide
- 77-6763
- Triton X 100
- Nitrous Acid, 77-6763

1,6-Hexanediol

- 1*H*-Azepine, Hexahydro-1-nitroso-
- Metabolism, Liver, 77-6764
- Nucleic Acids, 77-6764

2,5-Hexanedione

- Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
- Mitochondria, Liver, 77-6846
- Oxidative Phosphorylation, 77-6846

Hexanoic Acid, 6-Amino-

- Fibrin
- Cell Adhesion, 77-7183
- Surface Properties
- Ovary, Hamster, 77-7183

Hexoses

- Fibrosarcoma
- Basement Membrane, 77-7146

Histiocytes

- Granuloma
- Case Report, 77-7102
- Diagnosis and Prognosis, 77-7102

Histocompatibility Antigens

- Fibrosarcoma
- Virus, Polyoma, 77-7091
- Mammary Neoplasms, Experimental
- Hybrid Cells, 77-7087
- Neoplasms, Experimental
- Carcinogen, Chemical, 77-7090
- Virus, Murine Leukemia, 77-7090
- Plasmacytoma
- Antigenic Determinants, 77-7046
- Immune Response, 77-7046
- T-Lymphocytes, 77-7046
- Sarcoma
- Ethylene, Chloro- Polymer, 77-7035
- Foreign Bodies, 77-7035
- Hybrid Cells, 77-7087
- Virus, SV40, 77-7045
- Virus, Marek's Disease Herpes
- Graft vs Host Reaction, 77-7089
- Immune Response, 77-7089
- Virus, Murine Leukemia
- Immune Response, 77-7088
- Virus, Polyoma
- Embryo, Hamster, 77-7091
- Isolation and Characterization, 77-7091
- Virus, Radiation Leukemia
- Immune Response, 77-7088
- Virus, SV40
- Antigens, Neoplasm, 77-7084
- Cell Transformation, Neoplastic, 77-7070
- Temperature Sensitive Mutants, 77-7084

Histones

- Virus, SV40
- Isolation and Characterization, 77-7014

Hodgkin's Disease

- Adenocarcinoma
- Case Report, 77-6895
- Age Factors
- Epidemiology, 77-7154
- Carcinoma
- Case Report, 77-6895
- Coffee
- Epidemiology, 77-7154
- Communicable Diseases
- Epidemiology, 77-7154
- Epidemiology
- Histological Study, 77-7152
- Review, 77-7153
- Smoking, 77-7154
- Infectious Mononucleosis
- Epidemiology, 77-7152
- Lung Neoplasms
- Adenocarcinoma, 77-6895
- Carcinoma, 77-6895
- Case Report, 77-6895
- Spleen
- RNA, Viral, 77-6952
- Virus, Epstein-Barr
- Antigen-Antibody Reactions, 77-6994
- Virus, Rauscher Murine Leukemia
- DNA-RNA Hybridization, 77-6952
- Reverse Transcriptase, 77-6953

Hormone Antagonists

- Mammary Neoplasms, Experimental
- Prolactin, 77-6691

Hormones

- Breast Neoplasms
- Diet, 77-7162

Hyaluronic Acid

- Virus, Rous Sarcoma
- Cartilage, 77-6929
- Temperature Sensitive Mutants, 77-6928

Hybrid Cells

- L Cells
- Carcinogenic Potential, Mouse, Nude, 77-7037
- Cellulose, Methyl Ether, 77-7037
- Lymphocytes, 77-7037
- Transplantation Immunology, 77-7037
- Macrophages
- Ultrastructural Study, 77-7141
- Mammary Neoplasms, Experimental
- Chromosomes, 77-7087
- Histocompatibility Antigens, 77-7087
- Neoplasms, Experimental
- Karyotyping, 77-7140
- L Cells, 77-7140
- Mitosis, 77-7140
- Sarcoma
- Cholanthrene, 3-Methyl-, 77-7087
- Chromosomes, 77-7087
- Histocompatibility Antigens, 77-7087
- Virus, SV40
- Antigens, Viral, 77-7011
- Cell Aggregation, 77-7010
- Cell Transformation, Neoplastic, 77-7010, 77-7011
- 77-7013, 77-7141

Hybrid Cells (cont'd)

- Chromosomes, Human, 6-12, 77-7010
- Chromosomes, Human, 16-18, 77-7011
- DNA Replication, 77-7010
- Macrophages, 77-7141
- Temperature Sensitive Mutants, 77-7010
- Ultrastructural Study, 77-7141
- Virus Replication, 77-7013

Hydrazine

- Respiratory Tract Neoplasms
- Review, 77-6629

Hydrazine, 1,2-Dimethyl-

- Adenocarcinoma
- Cell Cycle Kinetics, 77-7174
- Colonic Neoplasms
- Adenocarcinoma, 77-6856
- Carcinogenic Potential, 77-6855
- Dietary Fats, 77-6797
- Genetics, 77-6855
- Ultrastructural Study, 77-6857
- Intestinal Neoplasms
- Adenocarcinoma, 77-7174
- Cell Cycle Kinetics, 77-7174

Hydrazine, 1,1-Diphenyl-

- Ozone
- Mutagenic Activity, 77-6798
- Water Pollutants
- Ozone, 77-6798

Hydrazine, Methyl-

- Carcinogenic Potential
- Mouse, 77-6854
- Metabolism
- Mouse, 77-6854

Hydro-Lyases

- Aryl Hydrocarbon Hydroxylases
- Liver, Rat, 77-6751

Hydrochloric Acid

- Acetohydroxamic Acid, *N*-Fluoren-2-yl-
- Hydroxylases, 77-6833

Hydroquinone

- Ozone
- Mutagenic Activity, 77-6798
- Water Pollutants
- Ozone, 77-6798

1-Hydroxybenzo(a)pyrene

- see Benzo(a)pyren-1-ol

3-Hydroxybenzo(a)pyrene

- see Benzo(a)pyren-3-ol

6-Hydroxybenzo(a)pyrene

- see Benzo(a)pyren-6-ol

Hydroxylases

- Acetohydroxamic Acid, *N*-Fluoren-2-yl-
- Acetamide, *N*-Fluoren-2-yl-, 77-6833
- Acetic Acid, Trifluoro-, Anhydride, 77-6833
- Barbituric Acid, 5-Ethyl-5-phenyl-, 77-6833
- Cholanthrene, 3-Methyl-, 77-6833
- Hydrochloric Acid, 77-6833
- Quantitation Method, 77-6833
- Benzo(a)pyrene
- Metabolism, Pancreas, 77-6741
- Kepone
- Liver, Rat, 77-6820

Hyperparathyroidism

- Thyroid Neoplasms
- Radiotherapy, 77-6632

Hyperplasia

- Benzo(a)pyren-2-ol
- Epidermis, Mouse, 77-6722
- Benzo(a)pyren-9-ol
- Epidermis, Mouse, 77-6722
- Benzo(a)pyrene
- Epidermis, Mouse, 77-6722
- Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-tetrahydro-
- Epidermis, Mouse, 77-6722
- Benzo(a)pyrene, 9,10-Oxy-7,8,9,10-tetrahydro-
- Epidermis, Mouse, 77-6722
- Liver Neoplasms
- Androgens, 77-6621
- Contraceptives, Oral, 77-6621
- Prostatic Neoplasms
- Testosterone, Propionate, *p*-Hexaphenyl-, 77-6877
- Vaginal Neoplasms
- Estradiol, 77-6875
- Progesterone, 77-6875

Hypersensitivity, Delayed

- Lymphoma
- Immune Response, 77-7032
- Sarcoma, Reticulum Cell
- Immune Response, 77-7032

Hypertension

- Kidney Neoplasms
- Adenocarcinoma, 77-7112
- Case Report, 77-7112

Hyperthyroidism

- Mammary Neoplasms, Experimental
- Iodine Radioisotopes, 77-6883
- Radiation, Ionizing, 77-6883

Hypoxanthine

- Virus, Epstein-Barr
- Antigens, Viral, 77-6994

IgD

- Leukemia, Hairy Cell
- Immunoglobulins, Surface, 77-7075

IgG

- Benzo(a)pyrene
- Antibody Formation, 77-7048
- Cell Transformation, Neoplastic
- Solid Tumors, Review, 77-6651
- Head and Neck Neoplasms
- Lymph Nodes, 77-7072
- Myeloma Proteins
- Binding, 77-7062
- Macrophages, 77-7062
- Virus, Avian Leukosis
- Immune Response, 77-6992

IgM

- Astrocytoma
- Transplantation Immunology, 77-7036
- Benzo(a)pyrene
- Antibody Formation, 77-7048
- Carcinoma
- Transplantation Immunology, 77-7036
- Cell Transformation, Neoplastic
- Solid Tumors, Review, 77-6651

IgM (cont'd)

- Fibrosarcoma
 - Transplantation Immunology, 77-7036
- Leukemia, Hairy Cell
 - Immunoglobulins, Surface, 77-7075
- Melanoma
 - Transplantation Immunology, 77-7036
- Nephroblastoma
 - Transplantation Immunology, 77-7036
- Rhabdomyosarcoma
 - Transplantation Immunology, 77-7036
- Virus, Avian Leukosis
 - Immune Response, 77-6992

Immune Serums

- Nasopharyngeal Neoplasms
 - Lymphotoxins, 77-7054
- Sarcoma, Osteogenic
 - Antibodies, 77-7031
 - Antigens, 77-7031
- Virus, C-Type RNA Tumor
 - Antigens, Viral, 77-6966
- Virus, Gross Murine Leukemia
 - Antigen-Antibody Reactions, 77-7043
- Virus, Murine Leukemia
 - Antibody Specificity, 77-7043
 - Antigen-Antibody Reactions, 77-7043
 - Viral Proteins, 77-6961

Immunity

- Sarcoma
 - Cholanthrene, 3-Methyl-, 77-7086

Immunity, Active

- Lung Neoplasms
 - Radiation, Ionizing, 77-7041
- Mammary Neoplasms, Experimental
 - Antigens, Neoplasm, 77-7041
 - Radiation, Ionizing, 77-7041
- Ovarian Neoplasms
 - Antigens, Neoplasm, 77-7041
 - Radiation, Ionizing, 77-7041

Immunity, Cellular

- Acetamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 - Dose-Response Study, Mouse, 77-7033
- Carcinoma
 - Immune Response, Humoral, 77-7063
- Head and Neck Neoplasms
 - Carcinoma, Epidermoid, 77-7071
 - Lymph Nodes, Regional, 77-7071
- Leukemia
 - Isotope Assay, 77-7050
 - Virus, Friend Murine Leukemia, 77-7050
- Leukemia, Lymphocytic
 - Acetamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
 - 77-7033
- Lymphocytes
 - Cytotoxicity, 77-7176
 - Effector Cells, 77-7051
 - Immunoglobulins, Fc, 77-7051
- Neoplasms, Experimental
 - Listeria monocytogenes*, 77-7047
 - Transplantation, Homologous, 77-7030
- Sarcoma
 - Reticuloendothelial System, 77-7047
- Sarcoma, Mast Cell
 - Antigens, Neoplasm, 77-7049
 - Chromium Release Assay, 77-7049

Immunity, Cellular (cont'd)

- Virus, Herpes Simplex 1
 - Antibodies, Viral, 77-7052, 77-7053
 - Effector Cell, Isolation and Characterization
 - 77-7052
 - Immunoglobulins, Fc, 77-7052
 - Lymphocyte Depletion, 77-7052
 - Lymphocytes, 77-7053
- Virus, Moloney Murine Sarcoma
 - Lymphocytes, 77-7176

Immunity, Passive

- T-Lymphocytes
 - Haptens, 77-7067
- Mammary Neoplasms, Experimental
 - Graft Rejection, 77-7034
- Teratoid Tumor
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-7044
 - Radiation, Ionizing, 77-7044

Immunoglobulins

- Agammaglobulinemia
 - Lymphocytes, 77-7064
- Cell Transformation, Neoplastic
 - Solid Tumors, Review, 77-6651
- Head and Neck Neoplasms
 - Lymph Nodes, 77-7072
- Leukemia, Lymphocytic
 - Cellular Inclusions, 77-7131
- Lymphoma
 - Streptodornase and Streptokinase, 77-7032
- Multiple Myeloma
 - Review, 77-6649
- Plasmacytoma
 - Review, 77-6649
- Sarcoma, Reticulum Cell
 - Immune Response, 77-7032

Immunoglobulins, Fc

- Leukemia, Myelocytic
 - Karyotyping, 77-7127
- Lymphocytes
 - Cytotoxicity, 77-7051
 - Immunity, Cellular, 77-7051
- Virus, Herpes Simplex 1
 - Immunity, Cellular, 77-7052

Immunoglobulins, Surface

- Carcinoma
 - Growth, 77-7063
 - Immune Response, Humoral, 77-7063
- Leukemia, Hairy Cell
 - IgD, 77-7075
 - IgM, 77-7075
 - Lymphocytes, 77-7132
- Sarcoma, Mast Cell
 - Growth, 77-7049

Immunologic Deficiency Syndromes

- Immune Response
 - Review, 77-6649
- Lymphoma
 - Virus, Epstein-Barr, 77-6646
- Neoplasms
 - Review, 77-6647

Immunosuppression

- Agammaglobulinemia
 - B-Lymphocytes, 77-7064
 - T-Lymphocytes, 77-7064

Immunosuppression (cont'd)

- Alkylating Agents
 - Carcinogenic Activity, Review, 77-6609
- Antimetabolites, Antineoplastic
 - Carcinogenic Activity, Review, 77-6609
- Antineoplastic Agents
 - Carcinogenic Activity, Review, 77-6609
- T-Lymphocytes
 - Antibody Formation, 77-7067
- Lymphoma
 - Diagnosis and Prognosis, 77-7032
- Mammary Neoplasms, Experimental
 - Graft Rejection, 77-7034
 - Neoplasm Metastasis, 77-7034
- Neoplasms
 - Review, 77-6647
- Sarcoma
 - Ethylene, Chloro- Polymer, 77-7035
 - Foreign Bodies, 77-7035
- Sarcoma, Reticulum Cell
 - Diagnosis and Prognosis, 77-7032

Indole-3-acetic Acid, 1-(*p*-Chlorobenzoyl)-5-methoxy-2-methyl-

- Cholanthrene, 3-Methyl-
 - Aryl Hydrocarbon Hydroxylases, 77-6755
- Skin Neoplasms
 - Cholanthrene, 3-Methyl-, 77-6755

Indole-3-acrylic Acid

- Neoplasms, Experimental
 - Animal Model, Guinea Pig, 77-6838
- Pancreatic Neoplasms
 - Islet Cell Tumor, 77-6838
- Peritoneal Neoplasms
 - Angiosarcoma, 77-6838

Infectious Mononucleosis

- Agammaglobulinemia
 - Immunodeficiency, 77-7121
- Hodgkin's Disease
 - Epidemiology, 77-7155
- Virus, Epstein-Barr
 - Epidemiology, 77-7155
 - Immunodeficiency, 77-7121
- Virus, Measles
 - Immunodeficiency, 77-7121

Insulin

- Breast Neoplasms
 - DNA Replication, 77-6865
 - Estradiol, 77-6865
- Mammary Neoplasms, Experimental
 - Estradiol, Ethinyl-11 α -methoxy-, 77-6695

Interferon

- Virus, Meningitis
 - Hematopoietic Stem Cells, 77-6944
 - Radiation, Ionizing, 77-6944
- Virus, Rauscher Murine Leukemia
 - Immune Response, 77-6949
 - Virus Replication, 77-6949

Intestinal Neoplasms

- Adenocarcinoma
 - Hydrazine, 1,2-Dimethyl-, 77-7174
- Genetics
 - Chromosome Abnormalities, 77-7105
- Hydrazine, 1,2-Dimethyl-
 - Cell Cycle Kinetics, 77-7174
- Methane, Azoxy-

Intestinal Neoplasms (cont'd)

- Rat, 77-6864
- Plasmacytoma
 - Rat, 77-7143
- Polyps
 - Genetics, 77-7105

Intestines

- Aflatoxin B1
 - Tissue Distribution, 77-6669

Iodine Radioisotopes

- Bone Neoplasms
 - Strontium Radioisotopes, 77-6884
- Mammary Neoplasms, Experimental
 - Dose-Response Study, 77-6883
 - Hyperthyroidism, 77-6883
 - Radiation, Ionizing, 77-6883
- Thyroid Neoplasms
 - Epidemiology, Review, 77-6632
 - Histological Study, Review, 77-6632
 - Radioactive Fallout, 77-6882

Ionophore A23187

- Lymphocytes
 - Calcium, 77-7197

Iron

- Virus, Meningitis
 - Hematopoietic Stem Cells, 77-6944

Islet Cell Tumor

- Pancreatic Neoplasms
 - Indole-3-acrylic Acid, 77-6838
 - Sulfonic Acid, α -Alkene-, 77-6791

Isoantigens

- Leukemia, Lymphoblastic
 - B-Lymphocytes, 77-7078
- Leukemia, Lymphocytic
 - B-Lymphocytes, 77-7078
- Leukemia, Myelocytic
 - B-Lymphocytes, 77-7078
- Virus, Marek's Disease
 - Graft VS Host Reaction, 77-7089

Isoenzymes

- Aminotransferases
 - Cell Differentiation, 77-7015
 - Cell Transformation, Neoplastic, 77-7015
- Kidney Neoplasms
 - Virus, Herpes Lucke, 77-7194
- Smoking
 - Cells, Cultured, 77-6700

Isopropyl Alcohol

- Diethylamine, 1,1'-Dimethyl-*N*-nitroso-
 - Microsomes, Liver, 77-6777
- Urea, *N*-Nitroso-*N*-propyl-
 - Microsomes, Liver, 77-6777

Isoproterenol

- 12-*O*-Tetradecanoylphorbol-13-acetate
 - Adenosine Cyclic 3',5' Monophosphate, 77-6747

Kallikrein-Trypsin Inactivator

- Carcinoma 256, Walker
 - Immune Response, 77-7180
 - Neoplasm Metastasis, 77-7180

Karyotyping

- Chondrosarcoma
 - Cells, Cultured, 77-6990

Karyotyping (cont'd)

- Leukemia, Myelocytic
 - Cell Differentiation, 77-7127
 - Complement, 77-7127
 - Immunoglobulins, Fc, 77-7127
- Neoplasms, Experimental
 - Hybrid Cells, 77-7140
- Pituitary Neoplasms
 - Aniline, 2,4,6-Trimethyl-, 77-6849
- Virus, Rous Sarcoma
 - Cell Transformation, Neoplastic, 77-6930
 - Chick Embryo, 77-6930

Keponc

- Cytochrome P-450
 - Liver, Rat, 77-6820
- Cytochrome Reductases
 - Liver, Rat, 77-6820
- Hydroxylases
 - Liver, Rat, 77-6820
- Oxidoreductases
 - Dose-Response Study, Rat, 77-6820
 - Liver, Rat, 77-6820
- Oxidoreductases, *N*-Demethylating
 - Liver, Rat, 77-6820

17-Ketosteroids

- Prostatic Neoplasms
 - Adenocarcinoma, 77-6877

Kidney

- Acetic Acid, Lead Salt
 - Ultrastructural Study, Rat, 77-6811
- Arsanilic Acid
 - Ultrastructural Study, Rat, 77-6811
- Cadmium Chloride
 - Ultrastructural Study, Rat, 77-6811
- Streptozotocin
 - Guanyl Cyclase, 77-6779
- Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
 - Guanyl Cyclase, 77-6779

Kidney Neoplasms

- Acetic Acid, Lead Salt
 - Species Difference, 77-6805
 - Sulfanilamide, *N*-2-Thiazolyl-, 77-6805
- Adenocarcinoma
 - Acetic Acid, Lead Salt, 77-6805
 - Hypertension, 77-7112
 - Virus, Herpes Lucke, 77-7194
- Adenoma
 - Acetic Acid, Lead Salt, 77-6805
- Cadmium Sulfate
 - Precancerous Conditions, 77-6812
- Diethylamine, *N*-Nitroso-
 - Hepatectomy, 77-6769
 - Histological Study, Rat, 77-6769
 - Nicotinamide, 77-6768
- Dimethylamine, *N*-Nitroso-
 - Hepatectomy, 77-6769
 - Histological Study, Rat, 77-6769
- Hypertension
 - Case Report, 77-7112
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - MSH, 77-6872
- Virus, Herpes Lucke
 - Isoenzymes, 77-7194
 - Muramidase, 77-7194

L Cells

- Benzo(a)pyren-3-ol
 - Cell Survival, 77-6731
- Benzo(a)pyren-6-ol
 - Cell Survival, 77-6731
- Benzo(a)pyrene
 - Cell Survival, 77-6731
- Hybrid Cells
 - Carcinogenic Potential, Mouse, Nude, 77-7037
 - Cellulose, Methyl Ether, 77-7037
 - Transplantation Immunology, 77-7037
- Lymphocytes
 - Hybrid Cells, 77-7037
- Neoplasms, Experimental
 - Hybrid Cells, 77-7140
- Urea, Hydroxy-
 - DNA Replication, 77-6787

Lactate Dehydrogenase Isoenzymes

- Smoking
 - Histochemical Study, Vero Cells, 77-6700

Lead

- Leukemia
 - Food Contamination, 77-6613
- Metabolism
 - Monkey, 77-6804

Lecithins

- 1-Hexanamine, *N*-Hexyl-
 - Nitrous Acid, 77-6763

Leiomyoma

- Ovarian Neoplasms
 - Acetophenone, 2-Amino-, 77-6838

Leucine

- Mammary Neoplasms, Experimental
 - Estrus, 77-6702

Leukemia

- Chromosome Abnormalities
 - Precancerous Conditions, 77-6659
- Immunity, Cellular
 - Isotope Assay, 77-7050
- Lead
 - Food Contamination, 77-6613
- Lymphoma
 - Drug Therapy, 77-6659
- Mammary Neoplasms, Experimental
 - Precancerous Conditions, 77-7133
- Radiation, Ionizing
 - Epidemiology, Review, 77-6630
- Sarcoma
 - Virus, Avian Erythroblastosis, 77-6915
- Spleen
 - RNA, Viral, 77-6952
- Virus, Avian Leukosis
 - Virus Subgroup, 77-6918
- Virus, C-Type RNA Tumor
 - Review, 77-6642
- Virus, Feline Leukemia
 - Review, 77-6642
- Virus, Friend Murine Leukemia
 - Immunity, Cellular, 77-7050
- Virus, Rauscher Murine Leukemia
 - DNA-RNA Hybridization, 77-6952
- Virus, Xenotropic Murine Leukemia
 - Mouse, Nude, 77-6945
- Water, Heavy

Leukemia (cont'd)

Precancerous Conditions, 77-7138

Leukemia, Acute Granulocytic

see Leukemia, Myeloblastic

Leukemia, Hairy Cell

Immunoglobulins, Surface

IgD, 77-7075

IgM, 77-7075

Lymphocytes

Acid Phosphatase, 77-7132

Cell Differentiation, 77-7132

Complement, 77-7132

Immunoglobulins, Surface, 77-7132

Ultrastructural Study, 77-7132

B-Lymphocytes

Isolation and Characterization, 77-7132

Phagocytosis, 77-7075

Monocytes

Esterases, 77-7075

Plant Agglutinins

Lymphocyte Transformation, 77-7075

Pyrophosphatases

Isolation and Characterization, 77-7134

Spleen

Acid Phosphatase, 77-7134

Pyrophosphatases, 77-7134

Leukemia L1210

Concanavalin A

Immune Response, 77-7040

Glutaraldehyde

Immune Response, 77-7040

Leukemia, Lymphoblastic

Chromosome Aberrations

Case Report, 77-7129

B-Lymphocytes

Antigens, 77-7074

Isoantigens, 77-7078

T-Lymphocytes

Antigens, 77-7074

Leukemia, Lymphocytic

Acetamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-

Antibody Formation, 77-7033

Dose-Response Study, Mouse, 77-7033

Immunity, Cellular, 77-7033

Cellular Inclusions

Case Report, 77-7131

Immunoglobulins, 77-7131

Ultrastructural Study, 77-7131

DNA Replication

Lymphocyte Culture Test, Mixed, 77-7073

B-Lymphocytes

Antigens, 77-7079

Immune Response, 77-7079

Isoantigens, 77-7078

T-Lymphocytes

DNA Replication, 77-7073

Lymphocyte Culture Test, Mixed, 77-7073

Virus, Epstein-Barr

Antigen-Antibody Reactions, 77-6994

Leukemia, Myeloblastic

Antigens

T-Lymphocytes, 77-7074

Cells, Cultured

Review, 77-6642

Leukemia, Myeloblastic (cont'd)

Chromosome Aberrations

Case Report, 77-7129

Leukocytes

Cell-Cell Interaction, 77-7177

Thymidine Incorporation, 77-7177

B-Lymphocytes

Antigens, 77-7074

Plant Agglutinins

Thymidine Incorporation, 77-7177

Radiation

Thymidine Incorporation, 77-7177

Leukemia, Myelocytic

Cell Differentiation

Chromosome Aberrations, 77-7127

Karyotyping, 77-7127

Cells, Cultured

Review, 77-6642

Cholanthrene, 3-Methyl-

Chromosome Aberrations, 77-7130

Chromosome Aberrations

Cell Transformation, Neoplastic, 77-7127

G-Banding, 77-7130

Mitosis, 77-7130

Chromosomes, Human, 21-22

Macrophages, 77-7128

Mitosis, 77-7128

Complement

Karyotyping, 77-7127

Erythrocytes

Isolation and Characterization, 77-7077

Immunoglobulins, Fc

Karyotyping, 77-7127

B-Lymphocytes

Isoantigens, 77-7078

Lymphoma

Case Report, 77-7126

Cyclophosphamide, 77-7126

Radiation, Ionizing

Case Report, 77-6886

Precancerous Conditions, 77-6893

Leukemia, Myelomonocytic

see Leukemia, Myelocytic

Leukemia, Radiation-Induced

Radiation, Ionizing

Virus Replication, 77-6962

Virus, Murine Leukemia

Antigens, Viral, 77-6962

Bone Marrow Cells, 77-6962

Precancerous Conditions, 77-6962

Thymus Neoplasms, 77-6962

Virus Replication, 77-6962

Leukocytes

Fibrosarcoma

Chemotaxis, 77-7059

Leukemia, Myeloblastic

Cell-Cell Interaction, 77-7177

Thymidine Incorporation, 77-7177

Leukocytosis

Mammary Neoplasms, Experimental

Neoplasm Transplantation, 77-7133

Leukoencephalopathy, Progressive Multifocal

Virus, Polyoma, JC

Antigens, Viral, 77-6984

Leydig Cell Tumor**FSH**

Gonadotropins, Pituitary, 77-6806

LH

Gonadotropins, Pituitary, 77-6806

LHBenz(a)anthracene, 7,12-Dimethyl-
Plasma Levels, 77-6695**FSH**

Gonadotropins, Pituitary, 77-6806

Leydig Cell Tumor

Gonadotropins, Pituitary, 77-6806

Teratoid Tumor

Gonadotropins, Pituitary, 77-6806

LH-FSH Releasing Hormone

Mammary Neoplasms, Experimental

Benz(a)anthracene, 7,12-Dimethyl-, 77-6691

Lip NeoplasmsDipropylamine, 2,2'-Diaceoxy-*N*-nitroso-
Hamster, 77-6762

Histological Study, 77-6762

2-Propanol, 1,1'-Iminodi-*N*-nitroso-
Hamster, 77-6762

Histological Study, 77-6762

LipidsPhorbol-12,13-dibenzoate
Cell Differentiation, 77-67484 α -Phorbol-12,13-didecanoate
Cell Differentiation, 77-674812-*O*-Tetradecanoylphorbol-13-acetate
Cell Differentiation, 77-6748**Lipopolysaccharides**

Neoplasms, Experimental

Transplantation, Homologous, 77-7030

Liposarcoma

Transplantation, Heterologous

Virus Replication, 77-6976

Virus, C-Type RNA Tumor

Virus Replication, 77-6976

Virus Replication

Ultrastructural Study, C-Type Particles, 77-6976

Listeria monocytogenes

Neoplasms, Experimental

Cholanthrene, 3-Methyl-, 77-7047

Immunity, Cellular, 77-7047

Reticuloendothelial System, 77-7047

Transplantation Immunology, 77-7047

Liver

Acetic Acid, Lead Salt

Ultrastructural Study, Rat, 77-6811

Aflatoxin B1

Metabolism, 77-6670

Metabolism, Mink, 77-6669

Proteins, 77-6668

Ribosomes, 77-6668

Tissue Distribution, 77-6669

Arsanilic Acid

Ultrastructural Study, Rat, 77-6811

Benzo(a)pyrene

Metabolism, Embryo, 77-6739

Metabolism, Mouse, 77-6733

Cadmium Chloride

Ultrastructural Study, Rat, 77-6811

Liver (cont'd)Dimethylamine, *N*-Nitroso-

Metabolism, Rat, 77-6774

Lymphosarcoma

Neoplasm Metastasis, 77-7125

Smoking

Cat, 77-6705

Metabolism, 77-6705

Rat, 77-6705

Liver Diseases

Ethylene, Chloro-

Occupational Hazard, Review, 77-6623

Liver NeoplasmsAcetamide, *N*-Fluoren-2-yl-

DNA, 77-6801

Fetal Globulins, 77-7109

Histological Study, Rat, 77-7109

Models, Biological, 77-6658

Acetamide, Thio-

RNA, Messenger, 77-6788

Acetohydroxamic Acid, *N*-Fluoren-2-yl-

Models, Biological, 77-6658

Adenoma

Case Report, 77-7110

Contraceptives, Oral, 77-7110

Estradiol, 17-Ethynyl-, 77-7110

Histological Study, 77-7110

Nitrous Acid, Sodium Salt, 77-6714

Aflatoxin B1

DNA, 77-6801

Models, Biological, 77-6658

Angiosarcoma

Ethylene, Chloro-, 77-6624, 77-6825

Occupational Hazard, 77-6622

Arsenic

Occupational Hazard, 77-6622

Barbituric Acid, 5-Ethyl-5-phenyl-

Acetamide, *N*-Fluoren-2-yl-, 77-6837Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-

Catalase, 77-6845

Fetal Globulins, 77-6848, 77-7109

Histological Study, 77-6845

Histological Study, Rat, 77-7109

Models, Biological, 77-6658

Rat, 77-6848

Ultrastructural Study, 77-6845

Cadmium Sulfate

Precancerous Conditions, 77-6812

Carcinoma

Acetamide, *N*-Fluoren-2-yl-, 77-6801

Aflatoxin B1, 77-6801

Diethylamine, *N*-Nitroso-, 77-6801

Epidemiology, 77-7160

Ethylene, Chloro-, 77-6825

Fetal Globulins, 77-7160

Cholangioma

Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-, 77-6814

Contraceptives, Oral

Dose-Response Study, 77-7159

Epidemiology, 77-7159

Mouse, 77-6866

p-Cresol, 2,6-Di-*tert*-butyl-Acetamide, *N*-Fluoren-2-yl-, 77-6837

Cystadenocarcinoma

Case Report, 77-7106

Histological Study, 77-7106

Liver Neoplasms (cont'd)

- Cystadenoma
 - Case Report, 77-7106
 - Histological Study, 77-7106
- Diethylamine, *N*-Nitroso-
 - Carcinogenic Activity, 77-6766
 - DNA, 77-6801
 - Hepatectomy, 77-6769
 - Histological Study, Rat, 77-6769
 - Mitotic Index, 77-6766
 - Models, Biological, 77-6658
 - Rat, 77-6612
- Dimethylamine, *N*-Nitroso-
 - Hepatectomy, 77-6769
 - Histological Study, Rat, 77-6769
 - Models, Biological, 77-6658
 - Rat, 77-6612
 - RNA, Messenger, 77-6788
- Dipropylamine, 2,2'-Diacetoxy-*N*-nitroso-
 - Hamster, 77-6762
- Estradiol, 17-Ethynyl-
 - Precancerous Conditions, 77-7159
- Ethylene, Chloro-
 - Occupational Hazard, 77-6622, 77-6825
 - Occupational Hazard, Review, 77-6623
- Food Contamination
 - Epidemiology, 77-6612
- Hamartoma
 - Contraceptives, Oral, 77-6621
- Hemangioendothelioma
 - Diethylamine, *N*-Nitroso-, 77-6801
- Hemangioma
 - Guanidine, Methyl-, 77-6714
 - Nitrous Acid, Sodium Salt, 77-6714
- Hyperplasia
 - Androgens, 77-6621
 - Contraceptives, Oral, 77-6621
- Mestranol
 - Mouse, 77-6866
- Methanol, (Methyl-*ONN*-azoxy)-
 - Models, Biological, 77-6658
- Morpholine, *N*-Nitroso-
 - Rat, 77-6612
- Mouse
 - Histological Study, 77-6866
- Mycotoxins
 - Food Contamination, 77-6612
- Nitrosamines
 - Food Contamination, 77-6612
- Nitrous Acid, Sodium Salt
 - Guanidine, Methyl-, 77-6714
- Norethynodrel
 - Mouse, 77-6866
- Piperidine, 1-Nitroso-
 - Rat, 77-6612
- Precancerous Conditions
 - Contraceptives, Oral, 77-7159
- Progesterone
 - Precancerous Conditions, 77-7159
- 2-Propanol, 1,1'-Iminodi-*N*-nitroso-
 - Hamster, 77-6762
- Streptozotocin
 - Adenoma, 77-6673
 - Histological Study, 77-6673
- Thorium Dioxide
 - Occupational Hazard, 77-6622

Liver Regeneration

- Cytosine, 1- β -*D*-Arabinofuranosyl-, Monohydrochloride
 - DNA Nucleotidyltransferases, 77-7190
- Novobiocin
 - DNA Nucleotidyltransferases, 77-7190

Lung

- Asbestos
 - Galactosidases, 77-6912
 - Glucosaminidase, 77-6912
 - Glucuronidase, 77-6912
 - Macrophages, Alveolar, 77-6912
- Benz(a)anthracene, 5,6-Dihydro-5,6-dihydroxy-
 - Metabolism, 77-6697
- Benz(a)anthracene, 8,9-Dihydro-8,9-dihydroxy-7-methyl-
 - Metabolism, 77-6697
- Benz(a)anthracene, 5,6-Dihydro,5,6-epoxy-7-methyl-
 - Metabolism, 77-6697
- Benz(a)anthracene, 7-Methyl-
 - Metabolism, 77-6697
 - Mouse, 77-6697
- Enzymes
 - Isolation and Characterization, 77-7195
- Epoxide Hydratases
 - Rat, 77-6753
- Fibrosarcoma
 - Basement Membrane, 77-7146
- Plutonium
 - Chromosome Aberrations, 77-6881

Lung Diseases, Obstructive

- Lung Neoplasms
 - Genetics, Review, 77-6661

Lung Neoplasms

- Adenocarcinoma
 - 2-Benzimidazolecarbamic Acid, Methyl Ester
 - 77-6786
 - Epidemiology, 77-7169
 - Guanidine, Dodecyl-, Acetate, 77-6786
 - Histochemical Study, 77-6736
 - Hodgkin's Disease, 77-6895
 - Plutonium Dioxide, 77-6880
 - Ultrastructural Study, 77-6736
 - Urea, Ethyl Nitroso-, 77-6897
- Adenoma
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-6683
 - Benzo(a)pyrene, 77-6683
 - Carbamic Acid, Ethyl Ester, 77-6878, 77-6879
 - Ethylene, Chloro-, 77-6624
 - Plutonium, 77-6879
 - 4,4'-Stilbenediol, α,α' -Diethyl-, 77-6869
 - Urea, Ethyl Nitroso-, 77-6897
- Air Pollution
 - Epidemiology, USSR, 77-6664
- Alpha Particles
 - Epidemiology, Review, 77-6630
- Aminotransferases
 - Isolation and Characterization, 77-7195
- Animal Model, Dog
 - Review, 77-6629
- Animal Model, Hamster
 - Review, 77-6629
- Asbestos
 - Epidemiology, 77-6914, 77-7173
 - Epidemiology, Review, 77-6627
- 2-Benzimidazolecarbamic Acid, Methyl Ester
 - Transplacental Carcinogenesis, 77-6786
- Benzo(a)pyrene

Lung Neoplasms (cont'd)

- Benzene, (2-Isothiocyantoethyl)-, 77-6683
- Benzene, (2-Isothiocyantomethyl)-, 77-6683
- Ultrastructural Study, 77-6736
- Carbamic Acid, Ethyl Ester
- Plutonium Oxide, 77-6878
- Carcinoma
 - Case Report, 77-7094
 - Drug Therapy, 77-6895
 - Histological Study, 77-6663, 77-7094
 - Hodgkin's Disease, 77-6895
 - Precancerous Conditions, 77-6895
 - Radiation, 77-6895
 - Review, 77-6663
 - Ultrastructural Study, 77-7094
- Carcinoma, Bronchiolar
 - Case Report, 77-7096
 - Genetics, 77-7096
 - Histological Study, 77-7096
- Carcinoma, Bronchogenic
 - Case Report, 77-7093
 - Genetics, 77-7093
 - Histological Study, 77-6663
- Carcinoma, Epidermoid
 - Case Report, 77-7095
 - Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-, 77-6814
 - Epidemiology, 77-7169
 - Histological Study, 77-7095
 - Plutonium Oxide, 77-6880
 - Smoking, 77-6663
 - Ultrastructural Study, 77-6736
- Carcinoma, Oat Cell
 - Histological Study, 77-6663
- Carcinoma 256, Walker
 - Neoplasm Metastasis, 77-7180
- Cell Line
 - Ultrastructural Study, 77-6736
- Coke
 - Epidemiology, 77-7170
- Dipropylamine, 2,2'-Diacetoxy-*N*-nitroso-Hamster, 77-6762
- Enzymes
 - Isolation and Characterization, 77-7195
- Guanidine, Dodecyl-, Acetate
 - Transplacental Carcinogenesis, 77-6786
- Histological Study
 - Epidemiology, 77-7169
 - Review, 77-7169
- Hodgkin's Disease
 - Case Report, 77-6895
- Lung Diseases, Obstructive
 - Genetics, Review, 77-6661
- Lymphocytes
 - Aryl Hydrocarbon Hydroxylases, 77-6757
- Macrophages
 - Aryl Hydrocarbon Hydroxylases, 77-6757
- Mammary Neoplasms, Experimental
 - Benzene, (2-Isothiocyantoethyl)-, 77-6683
 - Benzene, (2-Isothiocyantomethyl)-, 77-6683
- Morpholine, *N*-Nitroso-Rat, 77-6629
- Mucus
 - Mucous and Serous Cells, Review, 77-6662
 - Synthesis, Review, 77-6662
- Occupational Hazard
 - Epidemiology, 77-7168
- Plutonium Oxide

Lung Neoplasms (cont'd)

- Aerosols, 77-6880
 - Dose-Response Study, Rat, 77-6880
 - Inhalation Study, Mouse, 77-6878
 - Pneumoconiosis
 - Epidemiology, 77-7170
 - Polonium
 - Ultrastructural Study, 77-6736
 - 2-Propanol, 1,1'-Iminodi-*N*-nitroso-Hamster, 77-6762
 - Radiation, Ionizing
 - Histological Study, Hamster, 77-7041
 - Immunity, Active, 77-7041
 - Rat
 - Review, 77-6629
 - Smoking
 - Aryl Hydrocarbon Hydroxylases, 77-6757
 - Epidemiology, USSR, 77-6664
 - Mouse, 77-6703
 - 4,4'-Stilbenediol, α,α' -Diethyl-Mouse, 77-6869
 - Transplacental Carcinogenesis, 77-6869
 - Thymidine Kinase
 - Isolation and Characterization, 77-7195
 - Transplantation, Heterologous
 - Virus Replication, 77-6976
 - Ultrastructural Study
 - Histochemical Study, 77-6736
 - Urea, Ethyl Nitroso-Transplacental Carcinogenesis, 77-6897
 - Virus, C-Type RNA Tumor
 - Virus Replication, 77-6976
 - Virus Replication
 - Ultrastructural Study, C-Type Particles, 77-6976
- Lymph Nodes**
- Cholanthrene, 3-Methyl-DNA Replication, 77-6680
 - Head and Neck Neoplasms
 - IgG, 77-7072
 - Immunoglobulins, 77-7072
 - T-Lymphocytes, 77-7072
- Lymphatic Diseases**
- Lymphocytes
 - Immunodeficiency, 77-7121
 - Virus, Epstein-Barr
 - Immunodeficiency, 77-7121
 - Virus, Measles
 - Immunodeficiency, 77-7121
- Lymphocyte Depletion**
- Virus, Herpes Simplex 1
 - Immunity, Cellular, 77-7052
 - Virus, Marek's Disease Herpes
 - T-Lymphocytes, 77-7065
 - Virus, Murine Mammary Tumor
 - Immune Response, 77-7066
 - T-Lymphocytes, 77-7066
- Lymphocyte Transformation**
- Leukemia, Hairy Cell
 - Plant Agglutinins, 77-7075
- Lymphocytes**
- Agammaglobulinemia
 - Erythropoiesis, 77-7064
 - Immunoglobulins, 77-7064
 - Astrocytoma
 - Transplantation Immunology, 77-7036

Lymphocytes (cont'd)

- Carcinoma
 - Transplantation Immunology, 77-7036
- Cell Transformation, Neoplastic
 - Immune Response, 77-6648
- Cholanthrene, 3-Methyl-
 - DNA Replication, 77-6680
- Chromic Acid
 - Chromosome Aberrations, 77-6803
- Chromium Oxide
 - Chromosome Aberrations, 77-6803
- Chromosome Aberrations
 - Radiation, Ionizing, 77-6902
- Colonic Neoplasms
 - Carcinoma, 77-7076
- Dichromic Acid, Disodium Salt
 - Chromosome Aberrations, 77-6803
- Fibrosarcoma
 - Transplantation Immunology, 77-7036
- Head and Neck Neoplasms
 - Concanavalin A, 77-7071
 - Plant Agglutinins, 77-7071
- Immunity, Cellular
 - Cytotoxicity, 77-7176
 - Effector Cells, 77-7051
- Immunoglobulins, Fc
 - Cytotoxicity, 77-7051
 - Immunity, Cellular, 77-7051
- Ionophore A23187
 - Calcium, 77-7197
- L Cells
 - Hybrid Cells, 77-7037
- Leukemia, Hairy Cell
 - Acid Phosphatase, 77-7132
 - Cell Differentiation, 77-7132
 - Complement, 77-7132
 - Immunoglobulins, Surface, 77-7132
 - Ultrastructural Study, 77-7132
- Lung Neoplasms
 - Aryl Hydrocarbon Hydroxylases, 77-6757
- Lymphatic Diseases
 - Immunodeficiency, 77-7121
- Macrophages
 - Chemotaxis, 77-7060
- Melanoma
 - Transplantation Immunology, 77-7036
- Methane, Sulfinylbis-
 - Cryopreservation, 77-7176
- Mitomycin C
 - Cell Transformation, Neoplastic, 77-7070
- Nephroblastoma
 - Transplantation Immunology, 77-7036
- Ovalbumin
 - Cell Movement, 77-7080
 - Chemotaxis, 77-7080
- Radiation
 - Cell Cycle Kinetics, 77-6898
 - DNA Nucleotidyltransferases, 77-6898
 - DNA Replication, 77-6898
 - Thymidine Kinase, 77-6898
- Receptors, Hormone
 - Glucocorticoids, 77-7198
- Rhabdomyosarcoma
 - Transplantation Immunology, 77-7036
- Serum Albumin
 - Cell Movement, 77-7080
 - Chemotaxis, 77-7080

Lymphocytes (cont'd)

- Smoking
 - Aryl Hydrocarbon Hydroxylases, 77-6757
- Thymoma
 - Agammaglobulinemia, 77-7064
- Ultraviolet Rays
 - Immune Response, Mouse, Review, 77-6637
- Virus, Bovine Leukemia
 - Antigens, Viral, 77-6938
 - Concanavalin A, 77-6938
- Virus, Epstein-Barr
 - Ultrastructural Study, 77-6996
- Virus, Herpes Simplex 1
 - Immunity, Cellular, 77-7053
- Virus, Moloney Murine Sarcoma
 - Cryopreservation, 77-7176
 - Immunity, Cellular, 77-7176
 - Methane, Sulfinylbis-, 77-7176
- Virus, Murine Mammary Tumor
 - Antigens, Viral, 77-7081
- Virus, SV40
 - Cytotoxicity, 77-7070

B-Lymphocytes

- Agammaglobulinemia
 - Immunosuppression, 77-7064
- Antigens
 - Isolation and Characterization, 77-7079
- Glycoproteins
 - Isolation and Characterization, 77-7079
- Leukemia, Hairy Cell
 - Isolation and Characterization, 77-7132
 - Phagocytosis, 77-7075
- Leukemia, Lymphoblastic
 - Antigens, 77-7074
 - Isoantigens, 77-7078
- Leukemia, Lymphocytic
 - Antigens, 77-7079
 - Immune Response, 77-7079
 - Isoantigens, 77-7078
- Leukemia, Myeloblastic
 - Antigens, 77-7074
- Leukemia, Myelocytic
 - Isoantigens, 77-7078
- T-Lymphocytes
 - Helper Activity, 77-7067
- Lymphoma
 - Virus, Epstein-Barr, 77-6646
- Myeloma Proteins
 - Binding, 77-7062
- Neoplasms, Experimental
 - Transplantation, Homologous, 77-7030

T-Lymphocytes

- Agammaglobulinemia
 - Immunosuppression, 77-7064
- Antibody Formation
 - Helper Activity, 77-7067
- Fibrosarcoma
 - Transplantation Immunology, 77-7068
- Haptens
 - Immunity, Passive, 77-7067
- Head and Neck Neoplasms
 - Lymph Nodes, 77-7072
- Immune Response
 - Review, 77-6650
- Immunosuppression
 - Antibody Formation, 77-7067

T-Lymphocytes (cont'd)

- Leukemia, Lymphoblastic
 - Antigens, 77-7074
- Leukemia, Lymphocytic
 - DNA Replication, 77-7073
 - Lymphocyte Culture Test, Mixed, 77-7073
- Leukemia, Myeloblastic
 - Antigens, 77-7074
- B-Lymphocytes
 - Helper Activity, 77-7067
- Lymphoma
 - Virus, Marek's Disease Herpes, 77-7065
- Myeloma Proteins
 - Binding, 77-7062
- Neoplasms, Experimental
 - Transplantation, Homologous, 77-7030
- Plant Agglutinins
 - Transplantation Immunology, 77-7068
- Plasmacytoma
 - Histocompatibility Antigens, 77-7046
 - Immune Response, 77-7046
- Thymoma
 - Transplantation Immunology, 77-7068
- Virus, Marek's Disease Herpes
 - Immune Response, 77-7065
 - Lymphocyte Depletion, 77-7065
- Virus, Murine Mammary Tumor
 - Immune Response, 77-7066
 - Lymphocyte Depletion, 77-7066

Lymphoid Tissue

- Graft vs Host Reaction
 - Transplacental Carcinogenesis, 77-7038

Lymphoma (General and Unspecified)

- Alpha Particles
 - Epidemiology, Review, 77-6630
- Antigens
 - Immune Response, Hamster, 77-7045
- 2-Benzimidazolecarbamic Acid, Methyl Ester
 - Transplacental Carcinogenesis, 77-6786
- Guanidine, Dodecyl-, Acetate
 - Transplacental Carcinogenesis, 77-6786
- Hypersensitivity, Delayed
 - Immune Response, 77-7032
- Immunoglobulins
 - Streptodornase and Streptokinase, 77-7032
- Immunosuppression
 - Diagnosis and Prognosis, 77-7032
- Leukemia
 - Drug Therapy, 77-6659
- Leukemia, Myelocytic
 - Case Report, 77-7126
 - Cyclophosphamide, 77-7126
- Lymphocyte Count
 - Streptodornase and Streptokinase, 77-7032
- Precancerous Conditions
 - Case Report, 77-7123
- Reactive Lymphadenopathy
 - Case Report, 77-7123
- Streptodornase and Streptokinase
 - Immune Response, 77-7032
- Thymus Neoplasms
 - Urea, Methyl Nitroso-, 77-7142
- Virus, Epstein-Barr
 - Antigen-Antibody Reactions, 77-6994
 - Antigens, Viral, 77-6994
 - Immunodeficiency, 77-7121

Lymphoma (General and Unspecified) (cont'd)

- Immunologic Deficiency Syndromes, 77-6646
- B-Lymphocytes, 77-6646
- Virus, Marek's Disease Herpes
 - T-Lymphocytes, 77-7065
- Virus, Measles
 - Immunodeficiency, 77-7121
 - Virus-Like Particles, 77-7121
- Virus, Moloney Murine Leukemia
 - Antigens, Neoplasm, 77-7085
- Virus, Murine Leukemia
 - Mouse, AKR, 77-6963

Lymphoma, Lymphocytic
see Lymphosarcoma**Lymphopenia**

- Sarcoma, Reticulum Cell
 - Immune Response, 77-7032

Lymphosarcoma

- 2-Benzimidazolecarbamic Acid, Methyl Ester
 - Transplacental Carcinogenesis, 77-6786
- Cells, Cultured
 - Pig, 77-7124
 - Virus-Like Particles, C-Type, 77-7124
- Guanidine, Dodecyl-, Acetate
 - Transplacental Carcinogenesis, 77-6786
- Liver
 - Neoplasm Metastasis, 77-7125
- Transplantation, Homologous
 - Neoplasm Metastasis, 77-7125
- Ultrastructural Study
 - Pig, 77-7124
- Virus, Bovine Leukemia
 - Antigens, Viral, 77-6938
 - Concanavalin A, 77-6938
- Virus, C-Type RNA Tumor
 - Isolation and Characterization, Mouse, 77-6975
 - Reverse Transcriptase, 77-6975
- Virus, Feline Leukemia
 - Seroepidemiology, Review, 77-6640

Lysosomes

- Stomach Neoplasms
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6713

Macrophages

- Fibrosarcoma
 - Chemotaxis, 77-7059
- Hybrid Cells
 - Ultrastructural Study, 77-7141
- Leukemia, Myelocytic
 - Chromosomes, Human, 21-22, 77-7128
- Lung Neoplasms
 - Aryl Hydrocarbon Hydroxylases, 77-6757
- Lymphocytes
 - Chemotaxis, 77-7060
- Mycobacterium bovis*
 - Chemotaxis, 77-7059
- Myeloma Proteins
 - Binding, 77-7062
 - IgG, 77-7062
- Smoking
 - Aryl Hydrocarbon Hydroxylases, 77-6757
- Ultraviolet Rays
 - Immune Response, Mouse, Review, 77-6637
- Virus, SV40
 - Hybrid Cells, 77-7141

- Magnesium**
 Cells, Cultured
 Biological Transport, 77-7196
 Glucose
 Biological Transport, 77-7196
 Uridine
 Biological Transport, 77-7196
- Malate Dehydrogenase**
 Smoking
 Histochemical Study, Vero Cells, 77-6700
- Maleic Acid**
 Streptozotocin
 Glutathione, 77-6779
 Guanyl Cyclase, 77-6779
 Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
 Guanyl Cyclase, 77-6779
- Maleimide, N-Ethyl-**
 Streptozotocin
 Guanyl Cyclase, 77-6779
- Mammary Neoplasms, Experimental**
 Acetamide, *N*-(Acetyloxy)-*N*-fluoren-2-yl-
 Carcinogenic Activity, Mouse, 77-6834
 Acetamide, *N*-(Acetyloxy)-*N*-fluoren-3-yl-
 Carcinogenic Activity, Mouse, 77-6834
 Acetamide, *N*-Fluoren-2-yl-
 Carcinogenic Activity, Mouse, 77-6834
 Estradiol, 77-6834
 Ovariectomy, 77-6834
 Acetamide, *N*-Fluoren-3-yl-
 Carcinogenic Activity, Mouse, 77-6834
 Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 Carcinogenic Activity, Mouse, 77-6834
 Acetohydroxamic Acid, *N*-Fluoren-3-yl-
 Carcinogenic Activity, Mouse, 77-6834
 Adenocarcinoma
 Benz(a)anthracene, 7,12-Dimethyl-, 77-6702
 Dietary Fats, 77-6676
 Histological Study, 77-6702
 Adenofibroma
 Rotenone, 77-6677
 Adenosine Triphosphatase
 Ultrastructural Study, Mouse, 77-7192
 Alanine, 3-(3,4-Dihydroxyphenyl)-
 Prolactin, 77-6619
 Antigens, Neoplasm
 Immunity, Active, 77-7041
 Benz(a)anthracene, 7,12-Dimethyl-
 A-43818, 77-6691
 Benzene, Isocyanato-, 77-6683
 Benzene, (2-Isothiocyanatoethyl)-, 77-6683
 Benzene, (2-Isothiocyanatomethyl)-, 77-6683
 Diet, 77-7162
 Estradiol, Ethinyl-11 α -methoxy-, 77-6695, 77-6696
 LH-FSH Releasing Hormone, 77-6691
 Prolactin, 77-6619, 77-6693, 77-6694
 Prolactin Release Inhibiting Hormone, 77-6691
 Receptors, Hormone, 77-6692
 Thiocyanic Acid, Phenylmethyl Ester, 77-6683
 Carcinoma
 Adenosine Triphosphatase, 77-7192
 Cell Cycle Kinetics, 77-7175
 Ethylene, Chloro-, 77-6624
 Histological Study, 77-7178
 Sex Factors, Mouse, 77-7175
 Carcinoma, Scirrhus
- Mammary Neoplasms, Experimental (cont'd)**
 Adenosine Triphosphatase, 77-7192
 Cell Membrane
 Adenosine Triphosphatase, 77-7192
 Estradiol
 Inhibitory Effects, Review, 77-6618
 Neonate, Mouse, 77-6875
 Receptors, Hormone, 77-6692
 Estradiol, Ethinyl-11 α -methoxy-
 Estradiol, 77-6695, 77-6696
 Insulin, 77-6695
 Progesterone, 77-6695
 Prolactin, 77-6695, 77-6696
 Receptors, Hormone, 77-6695, 77-6696
 Somatotropin, 77-6695
 Estrus
 Leucine, 77-6702
 Thymidine, 77-6702
 Graft Rejection
 Vascular Reactions, 77-7034
 Hematopoiesis
 Kinetic Study, 77-7133
 Hybrid Cells
 Chromosomes, 77-7087
 Histocompatibility Antigens, 77-7087
 Immunity, Passive
 Graft Rejection, 77-7034
 Immunosuppression
 Graft Rejection, 77-7034
 Neoplasm Metastasis, 77-7034
 Iodine Radioisotopes
 Dose-Response Study, 77-6883
 Hyperthyroidism, 77-6883
 Leukemia
 Precancerous Conditions, 77-7133
 Lung Neoplasms
 Benzene, (2-Isothiocyanatoethyl)-, 77-6683
 Benzene, (2-Isothiocyanatomethyl)-, 77-6683
 Mitochondria
 Isolation and Characterization, 77-6677
 Oxidative Phosphorylation, 77-6677
 Ultrastructural Study, 77-6677
 Neoplasm Metastasis
 Alanine, 3-(3,4-Dihydroxyphenyl)-, 77-6619
 Vascular Reactions, 77-7034
 Neoplasm Transplantation
 Dietary Fats, 77-6676
 Leukocytosis, 77-7133
 Neutrophils, 77-7133
 Precancerous Conditions
 Mast Cells, 77-6899
 Progesterone
 Estradiol, 77-6875
 Neonate, Mouse, 77-6875
 Receptors, Hormone, 77-6692
 Prolactin
 Hormone Antagonists, 77-6691
 Receptors, Hormone, 77-6692, 77-6693
 Radiation, Ionizing
 Adenocarcinoma, 77-6899
 Carcinoma, 77-6899
 Carcinoma, Ductal, 77-6899
 Graft Rejection, 77-7034
 Histological Study, Hamster, 77-7041
 Hyperthyroidism, 77-6883
 Immunity, Active, 77-7041
 Iodine Radioisotopes, 77-6883

- Mammary Neoplasms, Experimental (cont'd)**
 Mast Cells, 77-6899
 Urea, Ethyl Nitroso-, 77-6897
- Stomach Neoplasms**
 Benzene, (2-Isothiocyanatoethyl)-, 77-6683
 Benzene, (2-Isothiocyanatomethyl)-, 77-6683
- Urea, Ethyl Nitroso-**
 Transplacental Carcinogenesis, 77-6897
- Virus, Feline Leukemia**
 Antigens, Viral, 77-6933
 Virus-Like Particles, 77-6933
- Virus, Murine Mammary Tumor**
 Actin, 77-6943
 Histological Study, 77-6867
 Virus, Vesicular Stomatitis, 77-6940
- Virus, RD-114**
 Antigens, Viral, 77-6933
 Virus-Like Particles, 77-6933
- D-Mannopyranoside, α -Methyl-**
 Hepatoma
 Concanavalin A, 77-7191
 Tyrosine Aminotransferase, 77-7191
- Medulloblastoma**
 Brain Neoplasms
 Virus, Polyoma, 77-6983
- Melanoma**
 IgM
 Transplantation Immunology, 77-7036
 Lymphocytes
 Transplantation Immunology, 77-7036
 Skin Neoplasms
 Epidemiology, 77-6636
 Epidemiology, Review, 77-6656
 Genetics, 77-6636
 Pigmentation, 77-6636
 Review, 77-6636
 Ultraviolet Rays, 77-6636
 Ultraviolet Rays
 Transplantation Immunology, Review, 77-6637
- Mesothelioma**
 Asbestos
 Epidemiology, Review, 77-6627
 Pleural Neoplasms
 Histological Study, 77-6663
- Mestranol**
 Liver Neoplasms
 Mouse, 77-6866
- Methane, Azoxy-**
 Colonic Neoplasms
 Rat, 77-6864
 Intestinal Neoplasms
 Rat, 77-6864
- Methane, Dichloro-**
 2-Benzimidazolecarbamic Acid, Methyl Ester
 Nitroso Compounds, 77-6786
- Methane, Sulfinylbis-**
 Erythroleukemia
 Cell Cycle Kinetics, 77-7179
 Cell Differentiation, 77-7179
 Chromatin, 77-7179
 DNA Replication, 77-7179
 Lymphocytes
 Cryopreservation, 77-7176
- Methane, Sulfinylbis- (cont'd)**
 Virus, Friend Murine Leukemia
 Reverse Transcriptase, 77-6956
 Virus, Moloney Murine Sarcoma
 Lymphocytes, 77-7176
- Methanesulfonic Acid, Ethyl Ester**
 Cell Transformation, Neoplastic
 Histological Study, Hamster, 77-6793
Salmonella typhimurium
 Mutagenic Activity, 77-6795
- Methanesulfonic Acid, Isopropyl Ester**
 Virus, Rauscher Murine Leukemia
 Hematopoietic Stem Cells, 77-6950
 Splenomegaly, 77-6950
- Methanesulfonic Acid, Methyl Ester**
 Cell Transformation, Neoplastic
 Histological Study, Hamster, 77-6793
Salmonella typhimurium
 Mutagenic Activity, 77-6795
- Methanol**
 Dimethylamine, *N*-Nitroso-
 Metabolism, Rat, 77-6775
 Virus, Epstein-Barr
 Antibodies, Viral, 77-7055
- Methanol, (Methyl-*ONN*-azoxy)-, Acetate**
 Colonic Neoplasms
 Dietary Fats, 77-6797
 NADH, NADPH Oxidoreductases
 Intestines, Rat, 77-6862
 Liver, Rat, 77-6862
 Metabolism, Rat, 77-6862
 Pyrazole
 Metabolism, Rat, 77-6862
- Methanol, (Methyl-*ONN*-azoxy)-**
 Cell Division
 Intestine, Rat, 77-6863
 Deacylation
 Intestine, Rat, 77-6863
 DNA Replication
 Intestine, Rat, 77-6863
 Liver Neoplasms
 Models, Biological, 77-6658
- Methionine**
 Hepatoma
 Diethylamine, *N*-Nitroso-, 77-6765
- Methionine, *S*-Adenosyl-**
 Butyric Acid, 2-Amino-4-(ethylthio)-
 Liver, Rat, 77-6790
- Methotrexate**
 Cell Transformation, Neoplastic
 Cells, Cultured, Review, 77-6608
- Methyl(acetoxymethyl)nitrosamine**
 see Methylamine, *N*-Nitroso-*N*-propoxy-
- N*-Methyl-*N*-formylhydrazine**
 see Hydrazine, Methylformyl-
- O*-Methylguanine**
 see Purine, 2-Amino-6-methoxy-
- Methylnitrosourethane**
 see Carbamic Acid, Methylnitroso-, Ethyl Ester

Methylprednisolone
see Pregna-1,4-diene-3,20-dione, 11B,17,21-Trihydroxy-6
A-meth

Methyltestosterone
see Androsta-1,4-dien-3-one, 17-Hydroxy-17-methyl-

Methylumbelliferone
see 2*H*-1-Benzopyran-2-one, 7-Hydroxy-4-methyl-

Mibolerone
see Estr-4-en-3-one, 7 α ,17-Dimethyl-17 β -Hydroxy

Microsomes
Benzo(a)pyrene
Metabolism, Pancreas, 77-6741

Microsomes, Liver
Acetohydroxamic Acid, *N*-Fluoren-2-yl-
Quantitation Method, 77-6833
Barbituric Acid, 5-Ethyl-5-phenyl-
Orotic Acid, 77-6678
Cholanthrene, 3-Methyl-
Orotic Acid, 77-6678
Cytochrome P-450
Oxygenases, 77-6813
Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-
Cytochrome P-450, 77-6813
Diethylamine, 1,1'-Dimethyl-*N*-nitroso-
Isopropyl Alcohol, 77-6777
Metabolism, Rat, 77-6777
Propyl Alcohol, 77-6777
Diphenylamine, *N*-Nitroso-
Carcinogenic Activity, 77-6760
Ethylene, Chloro-
Carcinogenic Activity, 77-6760
Folic Acid, *N*-Nitroso-
Carcinogenic Activity, 77-6760
Urea, *N*-Nitroso-*N*-propyl-
Isopropyl Alcohol, 77-6777
Propyl Alcohol, 77-6777

Microtubules
Virus, Adeno 5
Binding, 77-6985
Brain, Chick, 77-6985
Proteins, 77-6985

Migration Inhibitory Factor
Fibrosarcoma
Cells, Cultured, 77-7059
Cholanthrene, 3-Methyl-, 77-7059
Virus, Moloney Murine Leukemia
Antigens, Neoplasm, 77-7085

Mitochondria
Cholanthrene, 3-Methyl-
Oxidative Phosphorylation, 77-6800
Dimethylamine, *N*-Nitroso-
Oxidative Phosphorylation, 77-6800
Mammary Neoplasms, Experimental
Isolation and Characterization, 77-6677
Oxidative Phosphorylation, 77-6677
Ultrastructural Study, 77-6677

Mitochondria, Liver
Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
2,3-Butanediol, 1,4-Dimercapto-, 77-6846
2,3-Butanedione, 77-6846
2,5-Hexanedione, 77-6846
2,4-Pentanedione, 77-6846

Mitomycin C
Lymphocytes
Cell Transformation, Neoplastic, 77-7070

Mitosis
Dichromic Acid, Dipotassium Salt
Fibroblasts, 77-6803
Leukemia, Myelocytic
Chromosome Aberrations, 77-7130
Chromosomes, Human, 21-22, 77-7128
Neoplasms, Experimental
Hybrid Cells, 77-7140
Smoking
Mesenchyma, 77-6704

Mixed Function Oxidases
Nutrition
Cytochrome P-450, 77-6614
Enzymatic Activity, 77-6614
Metabolism, 77-6614

Monocytes
Aryl Hydrocarbon Hydroxylases
Genetics, 77-6756
Benzo(a)pyrene
Metabolism, 77-6740
Corynebacterium parvum
Chemotaxis, 77-7058
Leukemia, Hairy Cell
Esterases, 77-7075
Pyran
Chemotaxis, 77-7058

Morpholine, *N*-Nitroso-
Cells, Cultured
Mutagenic Activity, 77-6770
Glycogen Phosphorylase
Liver, Rat, 77-6709
Glycogenesis
Cell Transformation, Neoplastic, 77-6709
Liver, Rat, 77-6709
Hepatoma
Glycogenesis, 77-6708
Precancerous Conditions, 77-6708
Liver Neoplasms
Rat, 77-6612
Lung Neoplasms
Rat, 77-6629

Mouth Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-
Hamster, 77-6794
Diethylamine, *N*-Nitroso-
Hamster, 77-6794
Dimethylamine, *N*-Nitroso-
Hamster, 77-6794
Dipropylamine, 2,2'-Diacetoxy-*N*-nitroso-
Hamster, 77-6762
Papilloma, 77-6762
Histological Study
Hamster, 77-6794
Occupational Hazard
Epidemiology, 77-7168
2-Propanol, 1,1'-Iminodi-*N*-nitroso-
Hamster, 77-6762
Papilloma, 77-6762
Snuff
Hamster, 77-6794
Urea, Methyl Nitroso-
Hamster, 77-6794

MSH

- Kidney Neoplasms
 - 4,4'-Stilbenediol, α,α' -Diethyl-, 77-6872
- 4,4'-Stilbenediol, α,α' -Diethyl-Serum/Pituitary Levels, 77-6872

Mucopolysaccharides

- Virus, Rous Sarcoma
 - Cartilage, 77-6928
 - Cell Transformation, Neoplastic, 77-6928
 - Temperature Sensitive Mutants, 77-6928

Multiple Myeloma

- Case Report
 - Ultrastructural Study, 77-7122
- Cryoglobulins
 - Ultrastructural Study, 77-7122
- Immunoglobulins
 - Review, 77-6649
- Radiation, Ionizing
 - Epidemiology, Review, 77-6630
- Spleen
 - RNA, Viral, 77-6952
- Virus, Rauscher Murine Leukemia
 - DNA-RNA Hybridization, 77-6952

Muramidase

- Kidney Neoplasms
- Virus, Herpes Lucke, 77-7194

Mycobacterium bovis

- Macrophages
- Chemotaxis, 77-7059

Mycotoxins

- Aspergillus flavus*
 - Isolation and Characterization, 77-6671
- Liver Neoplasms
 - Food Contamination, 77-6612
- Neoplasms, Experimental
 - Diethylamine, *N*-Nitroso-, 77-6768

Myeloma Proteins

- IgG
 - Binding, 77-7062
 - Macrophages, 77-7062
- B-Lymphocytes
 - Binding, 77-7062
- T-Lymphocytes
 - Binding, 77-7062
- Macrophages
 - Binding, 77-7062

NADH, NADPH Oxidoreductases

- Acetamide, *N*-Fluorenyl-2-yl-
 - Enzymatic Activity, 77-6799
- Benz(a)anthracene, 7,12-Dimethyl-
 - Enzymatic Activity, 77-6799
- Methanol, (Methyl-*ONN*-azoxy)-, Acetate
 - Intestines, Rat, 77-6862
 - Liver, Rat, 77-6862
 - Metabolism, Rat, 77-6862

1-Naphthylamine

- Bladder
 - Metabolism, Dog, 77-6839

2-Naphthylamine

- Bladder
 - Metabolism, Dog, 77-6839

Nasopharyngeal Neoplasms

- Age Factors
 - Epidemiology, 77-7156
- Carcinoma
 - Epidemiology, 77-7156
 - Ultrastructural Study, 77-6996
 - Virus, Epstein-Barr, 77-6996, 77-6997, 77-7054
- Ethnic Groups
 - Epidemiology, 77-7156
- Immune Serums
 - Lymphotoxins, 77-7054
- Lymphocyte Cytotoxicity
 - Antibodies, 77-7054
- Sarcoma
 - Epidemiology, 77-7156
- Virus, Epstein-Barr
 - Antigen-Antibody Reactions, 77-6994, 77-7054
 - Antigen-Antibody Reactions, Review, 77-6645
 - Carcinogenic Potential, Review, 77-6645
 - Epidemiology, Review, 77-6644
 - Isolation and Characterization, 77-6996
 - Seroepidemiology, Review, 77-6643
 - Ultrastructural Study, 77-6997

Neoplasm Circulating Cells

- Fibrosarcoma
 - Basement Membrane, 77-7146
 - Collagen, 77-7146
- Hepatoma
 - Sarcoma, Yoshida, 77-7136
 - Transcerebral Passage, 77-7136
- Sarcoma, Yoshida
 - Transcerebral Passage, 77-7136

Neoplasm Metastasis

- Brain Neoplasms
 - Hepatoma, 77-7136
 - Sarcoma, Yoshida, 77-7136
- Breast Neoplasms
 - Alanine, 3-(3,4-Dihydroxyphenyl)-, 77-6619
- Carcinoma 256, Walker
 - Kallikrein-Trypsin Inactivator, 77-7180
- Ethyl Alcohol
 - Epidemiology, 77-7148
- Lung Neoplasms
 - Carcinoma 256, Walker, 77-7180
- Lymphosarcoma
 - Liver, 77-7125
 - Transplantation, Homologous, 77-7125
- Mammary Neoplasms, Experimental
 - Alanine, 3-(3,4-Dihydroxyphenyl)-, 77-6619
 - Immunosuppression, 77-7034
 - Vascular Reactions, 77-7034
- Skin Neoplasms
 - Carcinoma, Basal Cell, 77-7098
- Smoking
 - Epidemiology, 77-7148
- Socioeconomic Factors
 - Epidemiology, 77-7148
- Stomach Neoplasms
 - Guanidine, 1-Ethyl-3-nitro-1-nitroso-, 77-6711
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6711

Neoplasm Transplantation

- Hepatoma
 - Histological Study, 77-7108
- Mammary Neoplasms, Experimental
 - Dietary Fats, 77-6676
 - Leukocytosis, 77-7133

Neoplasm Transplantation (cont'd)

Neutrophils, 77-7133

Sarcoma

Dog, 77-7117

Virus, Herpes Simplex 2, 77-7003

Neoplasms (General and Unspecified)

Antigens, Neoplasm

Immune Response, 77-6647

Benzo(a)pyrene

Perylene, 77-6738

Dibenzo-*p*-dioxin, 2,3,7,8-Tetrachloro-

Rat, 77-6814

Diet

Epidemiology, Japan, 77-7163

Immunologic Deficiency Syndromes

Review, 77-6647

Immunology

Review, 77-6647

Immunosuppression

Review, 77-6647

Perylene

Salamander, 77-6738

Neoplasms, Experimental

Acetophenone, 2-Amino-

Animal Model, Guinea Pig, 77-6838

Ascorbic Acid

Dose-Response Study, 77-6679

Growth, 77-6679

Benz(a)anthracene

Carcinogenic Metabolite, 77-6699

Carcinogen, Chemical

Histocompatibility Antigens, 77-7090

Cholanthrene, 3-Methyl-

Ascorbic Acid, 77-6679

Listeria monocytogenes, 77-7047

Diethylamine, *N*-Nitroso-

Fusarium, 77-6768

Mycotoxins, 77-6768

Galactosyltransferases

Isolation and Characterization, Serum, 77-6980

Hybrid Cells

Karyotyping, 77-7140

Mitosis, 77-7140

Indole-3-acrylic Acid

Animal Model, Guinea Pig, 77-6838

L Cells

Hybrid Cells, 77-7140

Listeria monocytogenes

Immunity, Cellular, 77-7047

Reticuloendothelial System, 77-7047

Transplantation Immunology, 77-7047

Sarcoma

Cholanthrene, 3-Methyl-, 77-7047

Torulopsis glabrata

Phagocytosis, 77-7030

Transplantation, Homologous

Antibody Formation, 77-7030

Immunity, Cellular, 77-7030

Lipopolysaccharides, 77-7030

B-Lymphocytes, 77-7030

T-Lymphocytes, 77-7030

Phagocytosis, 77-7030

Plant Agglutinins, 77-7030

Torulopsis glabrata, 77-7030

Ultraviolet Rays

Transplantation Immunology, Review, 77-6637

Neoplasms, Experimental (cont'd)

Virus, Murine Leukemia

Antigens, Viral, 77-7090

Histocompatibility Antigens, 77-7090

Virus Replication, 77-6948

Virus, Polyoma

Galactosyltransferases, 77-6980

Virus, Rauscher Murine Leukemia

Virus, Murine Leukemia, 77-6948

Neoplasms, Multiple Primary

Androgens

Receptors, Hormone, Review, 77-6617

Breast Neoplasms

Genetics, 77-7113

Esophageal Neoplasms

Precancerous Conditions, 77-7104

Stomach Neoplasms, 77-7104

Estrogens

Receptors, Hormone, Review, 77-6617

Precancerous Conditions

Receptors, Hormone, Review, 77-6617

Progesterone

Receptors, Hormone, Review, 77-6617

Skin Neoplasms

Animal Model, Review, 77-6655

Precancerous Conditions, 77-6655

Stomach Neoplasms

Precancerous Conditions, 77-7104

Ultraviolet Rays

DNA Repair, 77-6903

Virus, Polyoma

Animal Model, Mouse, Review, 77-6639

Neoplasms, Soft Tissue

Angiosarcoma

Acetophenone, 2-Amino-, 77-6838

Nephroblastoma

Cell Differentiation

Tissue, Embryonic, 77-7111

Cells, Cultured

Cell Differentiation, 77-7111

IgM

Transplantation Immunology, 77-7036

Lymphocytes

Transplantation Immunology, 77-7036

Nervous System Neoplasms

Astrocytoma

Urea, 1-Butyl-1-nitroso-, 77-6778

Ependymoma

Urea, 1-Butyl-1-nitroso-, 77-6778

Glioma

Urea, 1-Butyl-1-nitroso-, 77-6778

Neurilemmoma

Urea, 1-Butyl-1-nitroso-, 77-6778

Urea, Methyl Nitroso-, 77-6780

Neuroblastoma

Urea, Methyl Nitroso-, 77-6780

Neurofibroma

Urea, Methyl Nitroso-, 77-6780

Oligodendroglioma

Urea, 1-Butyl-1-nitroso-, 77-6778

Urea, 1-Butyl-1-nitroso-

Transplacental Carcinogenesis, 77-6778

Urea, Methyl Nitroso-

Castration, 77-6780

Dienestrol, 77-6780

Neurilemmoma

- Nervous System Neoplasms
 - Urea, 1-Butyl-1-nitroso-, 77-6778
 - Urea, Methyl Nitroso-, 77-6780
- Radiation, Ionizing
 - Aging, 77-6901
 - Histological Study, Rat, 77-6901
- Spinal Cord Neoplasms
 - Radiation, Ionizing, 77-6901
- Urea, Ethyl Nitroso-
 - Chromosomes, 77-7137

Neuroblastoma

- Nervous System Neoplasms
 - Urea, Methyl Nitroso-, 77-6780
- Transplantation, Heterologous
 - Virus Replication, 77-6976
- Virus, C-Type RNA Tumor
 - Virus Replication, 77-6976
- Virus Replication
 - Ultrastructural Study, C-Type Particles, 77-6976

Neurofibroma

- Nervous System Neoplasms
 - Urea, Methyl Nitroso-, 77-6780
- Urea, Methyl Nitroso-
 - Dienestrol, 77-6780
- Virus, SV40
 - Chromosomes, 77-7139

Neuroglia

- Urea, Methyl Nitroso-
 - Cell Transformation, Neoplastic, 77-6784
 - Dose-Response Study, Hamster, 77-6784

Neutrophils

- Corynebacterium parvum*
 - Chemotaxis, 77-7058
- Mammary Neoplasms, Experimental
 - Neoplasm Transplantation, 77-7133
- Pyran
 - Chemotaxis, 77-7058

Nickel Sulfide

- Amino Acids
 - Dissolution Kinetics, 77-6807
- Dissolution Kinetics
 - Serum, Rat, 77-6807
- Serum Albumin
 - Dissolution Kinetics, 77-6807

Nicotinamide

- Kidney Neoplasms
 - Diethylamine, *N*-Nitroso-, 77-6768

Nicotine

- Cholanthrene, 3-Methyl-
 - Metabolism, 77-6705
- Nitrous Acid
 - Tobacco, 77-6707
- Smoking
 - Condensate, 77-6701
 - Hemoglobins, 77-6758
 - Metabolism, 77-6705

Nicotine, 1'-Demethyl-

- Nicotine, 1'-Nitroso-1'-demethyl-
 - Nitrosation Kinetics, 77-6707
- Nitrous Acid
 - Tobacco, 77-6707

Nicotine, 1'-Nitroso-1'-demethyl-

- Anabasine
 - Nitrosation Kinetics, 77-6707
- Nicotine, 1'-Demethyl-
 - Nitrosation Kinetics, 77-6707
- Respiratory Tract Neoplasms
 - Histological Study, Hamster, 77-6706

Nitric Acid

- Diet
 - Nitrosamines, Review, 77-6611
- Dimethylamine, *N*-Nitroso-
 - Metabolism, 77-6715
- Gastrointestinal System
 - Acetophenone, 2'-Amino-, 77-6716
- Metabolism
 - Rat, 77-6716
- Nitrosamines
 - Metabolism, 77-6715

Nitric Acid, Sodium Salt

- Urea, Butyl-
 - Transplacental Carcinogenesis, 77-6778

Nitrite

- see Nitrous Acid

N-(4-(5-Nitro-2-furyl)-2-thiazolyl)acetamide

- see Acetamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-

Nitrosamines

- Correlation, Carcinogenic Activity, Review
 - Mutagenic Activity, 77-6607
- Food Contamination
 - Quantitation Method, 77-6718
- Liver Neoplasms
 - Food Contamination, 77-6612
- Photolysis
 - Quantitation Method, 77-6718
- Ultraviolet Rays
 - Photolysis, 77-6718

Nitroso Compounds

- Diet
 - Metabolism, Review, 77-6611
- Stomach Neoplasms
 - Epidemiology, Review, 77-6611

N-Nitrosohexamethyleneimine

- see 1*H*-Azepine, Hexahydro-1-nitroso-

N-Nitrosornicotine

- see Nicotine, 1'-Nitroso-1'-Demethyl-

Nitrous Acid

- Diet
 - Nitrosamines, Review, 77-6611
- Dimethylamine
 - Nitrosamines, Review, 77-6611
- Dimethylamine, *N*-Nitroso-
 - Metabolism, 77-6715
- Gastrointestinal System
 - Metabolism, 77-6716
- Rat, 77-6716
- 1-Hexanamine, *N*-Hexyl-
 - 1-Decanaminium, *N,N,N*-Trimethyl-, Bromide 77-6763
- Lecithins, 77-6763
- Triton X 100, 77-6763
- Nicotine
 - Tobacco, 77-6707
- Nicotine, 1'-Demethyl-

Nitrous Acid (cont'd)

Tobacco, 77-6707

Nitrosamines

Metabolism, 77-6715

Piperidine

Nitrosamines, Review, 77-6611

Pyrrolidine

Nitrosamines, Review, 77-6611

Nitrous Acid, Sodium Salt**Angiosarcoma**

Guanidine, Methyl-, 77-6714

Antipyrene, 4-(Dimethylamino)-

γ -Tocopherol, 77-6717

α -Tocopherolquinone, 77-6717

Vitamin E, 77-6717

Ascorbic Acid

Gastric Juice, 77-6717

Bile Duct Neoplasms

Adenoma, 77-6714

Guanidine, Methyl-, 77-6714

Guanidine, Dodecyl-, Acetate

Nitroso Compounds, 77-6786

Hemangioma

Guanidine, Methyl-, 77-6714

Hepatoma

Guanidine, Methyl-, 77-6714

Liver Neoplasms

Adenoma, 77-6714

Guanidine, Methyl-, 77-6714

Hemangioma, 77-6714

Sarcoma

Guanidine, Methyl-, 77-6714

Vitamin E

Alanine Aminotransferase, 77-6717

Gastric Juice, 77-6717

Norepinephrine**Aging**

Neural Transmission, Review, 77-6653

Digestive System Neoplasms

Neural Transmission, Review, 77-6653

Norethynodrel**Liver Neoplasms**

Mouse, 77-6866

Orharman

Salmonella typhimurium

Mutagenic Activity, 77-6802

Ornicotine

see Nicotine, 1'-Demethyl-

Ovobiocin**Carcinoma, Bronchogenic**

DNA Nucleotidyltransferases, 77-7190

DNA Nucleotidyltransferases

Liver Regeneration, 77-7190

Nucleic Acids

1*H*-Azepine, Hexahydro-1-nitroso-

1,6-Hexanediol, 77-6764

Pancreatic Ducts

Tissue Culture, 77-7107

Virus, Polyoma

Fibroblasts, 77-6978

Nucleotides

Urea, Methyl Nitroso-

Carbamoylation, 77-6782

Nucleotides (cont'd)

Virus, SV40

Base Sequence, 77-7016

Nutrition**Cytochrome P-450**

Mixed Function Oxidases, 77-6614

Mixed Function Oxidases

Enzymatic Activity, 77-6614

Metabolism, 77-6614

Occupational Hazard**Alpha Particles**

Epidemiology, Review, 77-6630

Arsenic

Review, 77-7171

Asbestos

Epidemiology, Review, 77-6628

Bladder Neoplasms

Benzidine, 77-6853

Epidemiology, 77-7168

Bronchial Neoplasms

Epidemiology, 77-7168

Chromic Acid

Chromosome Aberrations, 77-6803

Chromium Oxide

Chromosome Aberrations, 77-6803

Dichromic Acid, Disodium Salt

Chromosome Aberrations, 77-6803

Ethylene, Chloro-

Epidemiology, 77-6825

Liver Neoplasms

Angiosarcoma, 77-6622

Arsenic, 77-6622

Ethylene, Chloro-, 77-6622, 77-6825

Thorium Dioxide, 77-6622

Lung Neoplasms

Epidemiology, 77-7168

Mouth Neoplasms

Epidemiology, 77-7168

Radiation, Ionizing

Epidemiology, Review, 77-6630

Testicular Neoplasms

Epidemiology, 77-7161

Tracheal Neoplasms

Epidemiology, 77-7168

Ochratoxin A

LD 50

Age Factors, Mouse, 77-6672

Odontogenic Cysts

Calcinosis

Ultrastructural Study, 77-7101

Odontogenic Tumor

Calcinosis

Ultrastructural Study, 77-7101

 α -Olefin Sulfonate

see Sulfonic Acid, α -Alkene-

Oligodendroglioma

Nervous System Neoplasms

Urea, 1-Butyl-1-nitroso-, 77-6778

Urea, Ethyl Nitroso-

Chromosomes, 77-7137

Oligonucleotides

Virus, Murine Leukemia

Isolation and Characterization, 77-6946

Oligonucleotides (cont'd)
 Virus, Recombinant, 77-6946

Oncogenic Viruses
 Reverse Transcriptase
 Ribonuclease, 77-6951

Organ Culture
 Bronchi
 Glycoproteins, 77-7092

Orotic Acid
 Barbituric Acid, 5-Ethyl-5-phenyl-
 Microsomes, Liver, 77-6678
 Cholanthrene, 3-Methyl-
 Microsomes, Liver, 77-6678

Osmium Tetroxide
 Endonucleases
 DNA Repair, 77-6906

Osteopetrosis
 Virus, Rous Sarcoma
 Virus Subgroup, 77-6918

Osteosarcoma
 see Sarcoma, Osteogenic

Ovalbumin
 Lymphocytes
 Cell Movement, 77-7080
 Chemotaxis, 77-7080

Ovarian Neoplasms
 Antigens, Neoplasm
 Immunity, Active, 77-7041
 Leiomyoma
 Metabolism, 77-6838
 Radiation, Ionizing
 Histological Study, Hamster, 77-7041
 Immunity, Active, 77-7041
 Urea, Ethyl Nitroso-, 77-6897
 Urea, Ethyl Nitroso-
 Transplacental Carcinogenesis, 77-6897

1,2-Oxathiolane, 2,2-Dioxide
Salmonella typhimurium
 Mutagenic Activity, 77-6795

2-Oxetanone
 Cell Transformation, Neoplastic
 Histological Study, Hamster, 77-6793

Oxidoreductases
 Dimethylamine, *N*-Nitroso-
 Enzymatic Activity, 77-6774
 Ethyl Alcohol
 Intestines, Rat, 77-6862
 Liver, Rat, 77-6862
 Kepone
 Dose-Response Study, Rat, 77-6820
 Liver, Rat, 77-6820

Oxidoreductases, *N*-Demethylating
 Kepone
 Liver, Rat, 77-6820

Oxygen
 Aniline
 Sludge, 77-6852
 Aniline, *N,N*-Dimethyl-
 Sludge, 77-6852
 Benzidine
 Sludge, 77-6852

Oxygen (cont'd)
 Benzidine, 3,3'-Dimethyl-
 Sludge, 77-6852
 Benzidine, Tetramethyl-
 Sludge, 77-6852

Oxygenases
 Cytochrome P-450
 Microsomes, Liver, 77-6813

Oxyphenbutazone
 see 3,5-Pyrazolidinedione, 4-Butyl-1-(*p*-hydroxyphenyl)-
 2-phenyl-

Ozone
 Acetic Acid, Nitrilotri-
 Mutagenic Activity, 77-6798
 Water Pollutants, 77-6798
 Ethyl Alcohol
 Mutagenic Activity, 77-6798
 Water Pollutants, 77-6798
 Hydrazine, 1,1-Diphenyl-
 Mutagenic Activity, 77-6798
 Water Pollutants, 77-6798
 Hydroquinone
 Mutagenic Activity, 77-6798
 Water Pollutants, 77-6798
 Phenol
 Mutagenic Activity, 77-6798
 Water Pollutants, 77-6798
 Toluene, 2,4-Dinitro-
 Mutagenic Activity, 77-6798
 Water Pollutants, 77-6798

Pactamycin
 Virus, Feline Leukemia
 Viral Proteins, 77-6936

Paget's Disease, Extra-Mammary
 Skin Neoplasms
 Epidemiology, Review, 77-6656

Pancreatic Ducts
 Precancerous Conditions
 Ultrastructural Study, 77-7107
 Tissue Culture
 Nucleic Acids, 77-7107
 Proteins, 77-7107
 Ultrastructural Study, 77-7107

Pancreatic Neoplasms
 Dipropylamine, 2,2'-Diacetoxy-*N*-nitroso-
 Hamster, 77-6762
 Islet Cell Tumor
 Indole-3-acrylic Acid, 77-6838
 Sulfonic Acid, α -Alkene-, 77-6791
 2-Propanol, 1,1'-Iminodi-*N*-nitroso-
 Hamster, 77-6762
 Sulfonic Acid, α -Alkene-
 Dose-Response Study, Rat, 77-6791

Papilloma
 Dipropylamine, 2,2'-Diacetoxy-*N*-nitroso-
 Mouth Neoplasms, 77-6762
 Vaginal Neoplasms, 77-6762
 2-Propanol, 1,1'-Iminodi-*N*-nitroso-
 Mouth Neoplasms, 77-6762
 Vaginal Neoplasms, 77-6762
 Respiratory Tract Neoplasms
 Ultrastructural Study, 77-7097
 Skin Neoplasms

- pilloma (cont'd)**
 Benz(a)anthracene, 7,12-Dimethyl-, 77-6685
 Ro 10-9359, 77-6685
 12-*O*-Tetradecanoylphorbol-13-acetate
 Precancerous Conditions, 77-6743
- rathyroid Neoplasms**
 Adenoma
 Case Report, 77-7119
 Radiation, Ionizing, 77-6885
- Pentanedione**
 Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-
 Mitochondria, Liver, 77-6846
 Oxidative Phosphorylation, 77-6846
- ptide Hydrolases**
 Carcinogen, Chemical
 Liver, Rat, 77-6859
 Cell Membrane
 Cell Transformation, Neoplastic, 77-6859
 Cell Transformation, Neoplastic
 Liver, Rat, 77-6859
- ptides**
 Virus, Avian Myeloblastosis
 Cells, Cultured, 77-6926
 Virus, Feline Leukemia
 Viral Proteins, 77-6936
 Virus, Rous Sarcoma
 Cells, Cultured, 77-6926
- itoneal Neoplasms**
 Angiosarcoma
 Indole-3-acrylic Acid, 77-6838
- ylene**
 Neoplasms
 Benzo(a)pyrene, 77-6738
 Salamander, 77-6738
 Salamanders
 Carcinogenic Activity, Sewage Sludge, 77-6738
- ticides**
 Cell Transformation, Neoplastic
 Animal Model, Review, 77-6601
- gocytosis**
 Asbestos, 77-6912
 Leukemia, Hairy Cell
 B-Lymphocytes, 77-7075
 Neoplasms, Experimental
Torulopsis glabrata, 77-7030
 Transplantation, Homologous, 77-7030
- nanthrene, 9,10-Dihydro-9,10-epoxy-**
 Aryl Hydrocarbon Hydroxylases
 Liver, Rat, 77-6751
- nethyl Isothiocyanate**
see Benzene, (2-Isothiocyanatoethyl)-
- mol**
 Ozone
 Mutagenic Activity, 77-6798
 Smoking
 Condensate, 77-6701
 Water Pollutants
 Ozone, 77-6798
- mol, (1,1-Dimethylethyl)-4-methoxy-**
 Benzo(a)pyren-1-ol
 Metabolism, Liver, Mouse, 77-6730
- Phenol, (1,1-Dimethylethyl)-4-methoxy- (cont'd)**
 Benzo(a)pyren-3-ol
 Metabolism, Liver, Mouse, 77-6730
 Benzo(a)pyrene
 Benzo(a)pyren-3-ol, 77-6730
 Carcinogenic Activity, 77-6728
 Carcinogenic Effect, 77-6730
 Charge-Transfer Complex, 77-6728
 Free Radicals, 77-6728
 Metabolism, Liver, Mouse, 77-6730
 Benzo(a)pyrene 4,5-Oxide
 Metabolism, Liver, Mouse, 77-6730
- Phenyl Isothiocyanate**
see Benzene, Isocyanato-
- Phorbol**
 Cells, Cultured
 Cell Differentiation, 77-6748
 Mutagenic Activity, Hamster, 77-6746
 Ultraviolet Rays
 Ouabain Resistance, 77-6746
 Thioguanine Resistance, 77-6746
- Phorbol-12,13-diacetate**
 Cells, Cultured
 Cell Differentiation, 77-6748
- Phorbol-12,13-dibenzoate**
 Cells, Cultured
 Cell Differentiation, 77-6748
 Lipids
 Cell Differentiation, 77-6748
- Phorbol-12,13-didecanoate**
 Cells, Cultured
 Cell Differentiation, 77-6748
- 4 α -Phorbol-12,13-didecanoate**
 Cells, Cultured
 Cell Differentiation, 77-6748
 Lipids
 Cell Differentiation, 77-6748
- Phorbol Myristate Acetate**
see 12-*O*-Tetradecanoylphorbol-13-acetate
- Phosphodiesterases**
 Dibutyl Cyclic AMP
 Cell Cycle Kinetics, 77-6750
- Phosphoproteins**
 Virus, Rous Sarcoma
 RNA, Viral, 77-6932
 Ultraviolet Rays, 77-6932
- Phosphorus**
 Polycythemia Vera
 Radioisotopes, 77-7135
- Pigmentation**
 Skin Neoplasms
 Melanoma, 77-6636
- Pinealoma**
 Brain Neoplasms
 Virus, Polyoma, 77-6983
- Piperidine**
 Nitrous Acid
 Nitrosamines, Review, 77-6611
- Piperidine, 1-Nitroso-**
 Digestive System Neoplasms

- Piperidine, 1-Nitroso- (cont'd)**
 Transplacental Carcinogenesis, 77-6759
 Liver Neoplasms
 Rat, 77-6612
 Maternal-Fetal Exchange
 Hamster, 77-6759
 Respiratory Tract Neoplasms
 Histological Study, Hamster, 77-6706
 Transplacental Carcinogenesis, 77-6759
Salmonella typhimurium
 Mutagenic Activity, 77-6761
- Piperonyl Butoxide**
 Benzidine
 Metabolism, Aquatic Organisms, 77-6796
 Benzo(a)pyrene
 Metabolism, Aquatic Organisms, 77-6796
 Ethylene, Chloro-
 Metabolism, Aquatic Organisms, 77-6796
- Pituitary Neoplasms**
 Adenoma
 Prolactin, 77-7120
 Aniline, 2,4,6-Trimethyl-
 Chromosome Abnormalities, 77-6849
 Karyotyping, 77-6849
 Prolactin
 Hormone Secretion, 77-7120
- Plant Agglutinins**
 Head and Neck Neoplasms
 Lymphocytes, 77-7071
 Leukemia, Hairy Cell
 Lymphocyte Transformation, 77-7075
 Leukemia, Myeloblastic
 Thymidine Incorporation, 77-7177
 T-Lymphocytes
 Transplantation Immunology, 77-7068
 Neoplasms, Experimental
 Transplantation, Homologous, 77-7030
- Plant Tumors**
Agrobacterium tumefaciens
 Metabolism, 77-7186
- Plasmacytoma**
 Antigens, Neoplasm
 Immune Response, 77-7046
 Histocompatibility Antigens
 Antigenic Determinants, 77-7046
 Immune Response, 77-7046
 T-Lymphocytes, 77-7046
 Immunoglobulins
 Review, 77-6649
 Intestinal Neoplasms
 Rat, 77-7143
 T-Lymphocytes
 Immune Response, 77-7046
- Plasminogen**
 Teratoid Tumor
 Cell Aggregation, 77-7147
 Cell Differentiation, 77-7147
 Cells, Cultured, 77-7147
 Dibutyl Cyclic AMP, 77-7147
 Theophylline, 77-7147
 Toxins, 77-7147
- Pleural Effusion**
 Breast Neoplasms
 Carcinoma, 77-7114
- Pleural Effusion (cont'd)**
 Epidemiology, 77-7114
- Pleural Neoplasms**
 Asbestos
 Epidemiology, Review, 77-6627
 Fiber Glass
 Particle Size, 77-6911
 Mesothelioma
 Histological Study, 77-6663
 Sarcoma
 Fiber Glass, 77-6911
- Plutonium**
 Lung
 Chromosome Aberrations, 77-6881
 Lung Neoplasms
 Adenoma, 77-6879
- Plutonium Oxide**
 Lung Neoplasms
 Adenocarcinoma, 77-6880
 Aerosols, 77-6880
 Carbamic Acid, Ethyl Ester, 77-6878
 Carcinoma, Epidermoid, 77-6880
 Dose-Response Study, Rat, 77-6880
 Inhalation Study, Mouse, 77-6878
- Pneumoconiosis**
 Lung Neoplasms
 Epidemiology, 77-7170
- Polonium**
 Lung Neoplasms
 Ultrastructural Study, 77-6736
- Poly A**
 Acetohydroxamic Acid, *N*-Fluoren-2-yl-
 RNA, Ribosomal, 77-6832
- Polychlorobiphenyl Compounds**
 Metabolism
 Rat, 77-6816
- Polycyclic Hydrocarbons**
 Air Pollutants
 Mutagenic Activity, 77-6830
 Aroclor 1254
 Mutagenic Activity, 77-6830
 7,8-Benzoflavone
 Mutagenic Activity, 77-6830
 Respiratory Tract Neoplasms
 Review, 77-6629
Salmonella typhimurium
 Mutagenic Activity, 77-6830
- Polycythemia Vera**
 Bone Marrow Cells
 Erythropoiesis, 77-7199
 Dexamethasone
 Erythropoiesis, 77-7199
 Erythropoietin
 Erythropoiesis, 77-7199
 Phosphorus
 Radioisotopes, 77-7135
 Radiation, Ionizing
 Case Report, 77-7135
 Urticaria Pigmentosa
 Case Report, 77-7135

Polyphosphatidylcholine
see Lecithins

Polyps

- Genetics
- Chromosome Abnormalities, 77-7105
- Intestinal Neoplasms
- Genetics, 77-7105

Potassium Bichromate

see Dichromic Acid, Dipotassium Salt

Precancerous Conditions

- Bladder Neoplasms
- Carcinoma In Situ, 77-6657
- Breast Neoplasms
- Genetics, 77-7150
- Esophageal Neoplasms
- Neoplasms, Multiple Primary, 77-7104
- Genetics
- Epidemiology, Review, 77-7150
- Gynecologic Neoplasms
- 4,4'-Stilbenediol, α, α' -Diethyl-, 77-6870
- Hepatoma
- Morpholine, *N*-Nitroso-, 77-6708
- Kidney Neoplasms
- Cadmium Sulfate, 77-6812
- Leukemia
- Chromosome Abnormalities, 77-6659
- Mammary Neoplasms, Experimental, 77-7133
- Water, Heavy, 77-7138
- Leukemia, Myelocytic
- Radiation, Ionizing, 77-6893
- Leukemia, Radiation-Induced
- Virus, Murine Leukemia, 77-6962
- Liver Neoplasms
- Cadmium Sulfate, 77-6812
- Contraceptives, Oral, 77-7159
- Estradiol, 17-Ethynyl-, 77-7159
- Progesterone, 77-7159
- Lung Neoplasms
- Carcinoma, 77-6895
- Lymphoma
- Case Report, 77-7123
- Mammary Neoplasms, Experimental
- Mast Cells, 77-6899
- Neoplasms, Multiple Primary
- Receptors, Hormone, Review, 77-6617
- Pancreatic Ducts
- Ultrastructural Study, 77-7107
- Papilloma
- 12-*O*-Tetradecanoylphorbol-13-acetate, 77-6743
- Skin Neoplasms
- Benz(a)anthracene, 7,12-Dimethyl-, 77-6688
- Diagnosis, Review, 77-6656
- Neoplasms, Multiple Primary, 77-6655
- Retinol, Hexadecanoate, 77-6688
- Spinal Cord Neoplasms
- Radiation, Ionizing, 77-6901
- Stomach Neoplasms
- Guanidine, 1-Ethyl-3-nitro-1-nitroso-, 77-6711
- Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6711
- 77-6713
- Neoplasms, Multiple Primary, 77-7104
- Virus, SV40
- Chromosomes, 77-7139
- Water, Heavy
- Chromosome Aberrations, 77-7138

Pregnancy

- Graft vs Host Reaction
- Transplacental Carcinogenesis, 77-7038
- Virus, Feline Leukemia
- Horizontal Transmission, Review, 77-6641

Progesterone

- Animal Feed
- Toxicology, 77-6868
- Benz(a)anthracene, 7,12-Dimethyl-
- Prolactin, 77-6695
- Estradiol
- Co-carcinogenic Activity, Mouse, 77-6875
- Liver Neoplasms
- Precancerous Conditions, 77-7159
- Mammary Neoplasms, Experimental
- Estradiol, 77-6875
- Estradiol, Ethinyl-11 α -methoxy-, 77-6695
- Neonate, Mouse, 77-6875
- Neoplasms, Multiple Primary
- Receptors, Hormone, Review, 77-6617
- Receptors, Hormone
- Mammary Neoplasms, Experimental, 77-6692
- Vaginal Neoplasms
- Estradiol, 77-6875
- Hyperplasia, 77-6875
- Neonate, Mouse, 77-6875

Prolactin

- Benz(a)anthracene, 7,12-Dimethyl-
- Progesterone, 77-6695
- Breast Neoplasms
- Diet, 77-7162
- Estradiol, 77-6865
- Receptors, Hormone, 77-6865
- Mammary Neoplasms, Experimental
- Alanine, 3-(3,4-Dihydroxyphenyl)-, 77-6619
- Benz(a)anthracene, 7,12-Dimethyl-, 77-6619
- 77-6693, 77-6694
- Estradiol, Ethinyl-11 α -methoxy-, 77-6695, 77-6696
- Hormone Antagonists, 77-6691
- Receptors, Hormone, 77-6693
- Pituitary Neoplasms
- Adenoma, 77-7120
- Hormone Secretion, 77-7120
- Receptors, Hormone
- Mammary Neoplasms, Experimental, 77-6692

Prolactin Release Inhibiting Hormone

- Mammary Neoplasms, Experimental
- Benz(a)anthracene, 7,12-Dimethyl-, 77-6691

Proline, 4-Hydroxy-

- Fibrosarcoma
- Basement Membrane, 77-7146

Proline, 4-Hydroxy-1-nitroso-

- Salmonella typhimurium*
- Mutagenic Activity, 77-6761

Proline, 1-Nitroso-

- Salmonella typhimurium*
- Mutagenic Activity, 77-6761

Propane, 1,2-Epoxy-3-(*p*-nitrophenoxy)-

- Benzo(a)pyrene
- Transferases, 77-6732
- Cholanthrene, 3-Methyl-
- Transferases, 77-6732

- 2-Propanol, 1,1'-Iminodi-*N*-nitroso-**
 Lip Neoplasms
 Hamster, 77-6762
 Liver Neoplasms
 Hamster, 77-6762
 Histological Study, 77-6762
 Papilloma, 77-6762
- β -Propiolactone**
 see 2-Oxetanone
- Propyl Alcohol**
 Diethylamine, 1,1'-Dimethyl-*N*-nitroso-
 Microsomes, Liver, 77-6777
 Urea, *N*-Nitroso-*N*-propyl-
 Microsomes, Liver, 77-6777
- Propylamine, *N*-Methyl-*N*-nitroso-**
 Cells, Cultured
 Mutagenic Activity, 77-6770
- Prostatic Neoplasms**
 Adenocarcinoma
 Androstenedione, 77-6877
 Estrone, 77-6876
 17-Ketosteroids, 77-6877
 Rat, 77-6876
 Testosterone, Propionate, 77-6876
 Hyperplasia
 Testosterone, Propionate, *p*-Hexaphenyl-, 77-6877
 Testosterone, Propionate, *p*-Hexaphenyl-
 Metabolism, Rat, 77-6877
- Protein Kinase**
 Virus, Friend Murine Leukemia
 Translational Inhibitor, Isolation and Characteriza-
 tion, 77-7188
- Proteins**
 Aflatoxin B1
 Liver, 77-6668
 Cycloheximide
 Liver, Rat, 77-7184
 DNA
 Alkylation, 77-6824
 Ethane, 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)-
 Liver, Rat, 77-6822
 Ethylene, Chloro-
 Testis, Mouse, 77-6824
 Pancreatic Ducts
 Tissue Culture, 77-7107
 Spherocytosis, Hereditary
 Phosphorylation, 77-7185
 Virus, Adeno 5
 Microtubules, 77-6985
 Virus, Rous Sarcoma
 Cell Membrane, 77-6925
 Cell Transformation, Neoplastic, 77-6925
 Virus, SV40
 Isolation and Characterization, 77-7023, 77-7024
- Prothidium**
Salmonella typhimurium
 Mutagenic Activity, 77-6828
- Psoralen, 4,5',8-Trimethyl-**
 Virus, SV40
 DNA, Viral, 77-7025
- Purine, 2-Amino-6-methoxy-**
 Dimethylamine, *N*-Nitroso-
 Dose-Response Study, Rat, 77-6771
 Liver, Rat, 77-6771
- Pyran**
 Monocytes
 Chemotaxis, 77-7058
 Neutrophils
 Chemotaxis, 77-7058
- Pyrazole**
 Dimethylamine, *N*-Nitroso-
 Hepatotoxicity, Rat, 77-6775
 Metabolism, Rat, 77-6775
 Methanol, (Methyl-*ONN*-azoxy)-, Acetate
 Metabolism, Rat, 77-6862
- Pyrazole, 4-Methyl-**
 Dimethylamine, *N*-Nitroso-
 Metabolism, Rat, 77-6775
- 3,5-Pyrazolidinedione, 4-Butyl-1-(*p*-hydroxyphenyl)-2-phenyl-**
 Cholanthrene, 3-Methyl-
 Aryl Hydrocarbon Hydroxylases, 77-6755
 DNA, Binding, 77-6755
 Skin Neoplasms
 Cholanthrene, 3-Methyl-, 77-6755
- 1-Pyrenamine**
 Dimethylamine, *N*-Nitroso-
 Metabolism, Rat, 77-6775
- Pyrene**
Salmonella typhimurium
 Mutagenic Activity, 77-6802
- 9*H*-Pyrid(3,4-*b*)indole, 1-Methyl-**
Salmonella typhimurium
 Mutagenic Activity, 77-6802
- 5*H*-Pyrido(4,3-*b*)indole, 3-Amino-1,4-dimethyl-**
Salmonella typhimurium
 Mutagenic Activity, 77-6802
- 5*H*-Pyrido(4,3-*b*)indole, 3-Amino-1-methyl-**
Salmonella typhimurium
 Mutagenic Activity, 77-6802
- Pyrophosphatases**
 Leukemia, Hairy Cell
 Isolation and Characterization, 77-7134
 Spleen, 77-7134
- 1*H*-Pyrrole-2,5-dione, 1-Ethyl-**
 Sarcoma
 DNA Replication, 77-7189
 Spherocytosis, Hereditary
 Phosphorylation, 77-7185
 Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-
 Guanyl Cyclase, 77-6779
- Pyrrolidine**
 Nitrous Acid
 Nitrosamines, Review, 77-6611
- Pyrrolidine, 3-Hydroxy-1-nitroso-**
Salmonella typhimurium
 Mutagenic Activity, 77-6761
- Pyrrolidine, 1-Nitroso-**
 Cells, Cultured
 Mutagenic Activity, 77-6770
Salmonella typhimurium
 Mutagenic Activity, 77-6761
- Quinoline, 4-Nitro-, 1-Oxide**
 Cell Transformation, Neoplastic
 Strain Difference, Mouse, 77-7144
 Cells, Cultured

Quinoline, 4-Nitro-, 1-Oxide (cont'd)

- Chromosome Aberrations, 77-6861
- DNA Replication, 77-6861
- Chromosome Aberrations
 - Species Difference, 77-6861
- Contact Inhibition
 - Cell Transformation, Neoplastic, 77-7144
- DNA Repair
 - Cell Transformation, Neoplastic, 77-6858
 - Cells, Cultured, 77-6792
- DNA Replication
 - Species Difference, 77-6861
- Embryo
 - Carcinogenic Activity, Mouse, 77-6860
 - Teratogenic Activity, Mouse, 77-6860
- Salmonella typhimurium*
 - DNA Repair, 77-6749
 - Mutagenic Activity, 77-6749, 77-6795, 77-6802
- Virus, Rauscher Murine Leukemia
 - Cell Transformation, Neoplastic, 77-6858
 - DNA Repair, 77-6858

Radiation

- Leukemia, Myeloblastic
 - Thymidine Incorporation, 77-7177
- Lung Neoplasms
 - Carcinoma, 77-6895
- Lymphocytes
 - Cell Cycle Kinetics, 77-6898
 - DNA Nucleotidyltransferases, 77-6898
 - DNA Replication, 77-6898
 - Thymidine Kinase, 77-6898

Radiation, Ionizing

- Angiosarcoma
 - Hemangioma, 77-6894
- Cervix Neoplasms
 - Carcinoma, Epidermoid, 77-6892
- Chromosome Aberrations
 - Lymphocytes, 77-6902
- DNA
 - DNA Repair, 77-6675
- Dose-Response Study
 - Risk Factors, Review, 77-6631
- Endonucleases
 - DNA Repair, 77-6906
- Environmental Hazard
 - Dose-Response Study, 77-6896
- Head and Neck Neoplasms
 - Angiosarcoma, 77-6894
- Leukemia
 - Epidemiology, Review, 77-6630
- Leukemia, Myelocytic
 - Case Report, 77-6886
 - Precancerous Conditions, 77-6893
- Leukemia, Radiation-Induced
 - Virus Replication, 77-6962
- Light
 - DNA, Electron Spin Resonance Study, 77-6900
 - Nucleosides, Radical Content, 77-6900
- Lung Neoplasms
 - Histological Study, Hamster, 77-7041
 - Immunity, Active, 77-7041
- Mammary Neoplasms, Experimental
 - Adenocarcinoma, 77-6899
 - Carcinoma, 77-6899
 - Carcinoma, Ductal, 77-6899
 - Graft Rejection, 77-7034

Radiation, Ionizing (cont'd)

- Histological Study, Hamster, 77-7041
- Hyperthyroidism, 77-6883
- Immunity, Active, 77-7041
- Iodine Radioisotopes, 77-6883
- Mast Cells, 77-6899
- Urea, Ethyl Nitroso-, 77-6897
- Multiple Myeloma
 - Epidemiology, Review, 77-6630
- Neurilemmoma
 - Aging, 77-6901
 - Histological Study, rat, 77-6901
- Nuclear Reactors
 - Risk Factors, Review, 77-6631
- Occupational Hazard
 - Epidemiology, Review, 77-6630
- Ovarian Neoplasms
 - Histological Study, Hamster, 77-7041
 - Immunity, Active, 77-7041
- Parathyroid Neoplasms
 - Adenoma, 77-6885
- Polycythemia Vera
 - Case Report, 77-7135
- Spinal Cord
 - Nerve Degeneration, 77-6901
- Spinal Cord Neoplasms
 - Histological Study, Rat, 77-6901
 - Neurilemmona, 77-6901
 - Precancerous Conditions, 77-6901
- Teratoid Tumor
 - Cell Differentiation, 77-7044
 - Immunity, Passive, 77-7044
- Thyroid Neoplasms
 - Adenoma, 77-6635, 77-6889
 - Carcinoma, 77-6633, 77-6634, 77-6635, 77-6885
 - 77-6889, 77-6890, 77-6891
 - Dose-Response Study, 77-6888
 - Epidemiology, 77-6885, 77-6887, 77-6888, 77-6890
 - Histological Study, 77-6889
- Vaginal Neoplasms
 - Carcinoma, Epidermoid, 77-6892
 - Carcinoma In Situ, 77-6892
- Virus, Meningitis
 - Interferon, 77-6944

Radioactive Fallout

- Thyroid Neoplasms
 - Adenoma, 77-6882
 - Dose-Response Study, 77-6882
 - Epidemiology, Marshall Islands, 77-6882
 - Iodine Radioisotopes, 77-6882

Radioisotopes

- Polycythemia Vera
 - Phosphorus, 77-7135
- Sarcoma, Osteogenic
 - Transplantation, Homologous, 77-7039

Receptors, Hormone

- Breast Neoplasms
 - Prolactin, 77-6865
- Estradiol
 - Mammary Neoplasms, Experimental, 77-6692
- Lymphocytes
 - Glucocorticoids, 77-7198
- Mammary Neoplasms, Experimental
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-6692
 - Estradiol, Ethinyl-11 α -methoxy-, 77-6695, 77-6696
 - Prolactin, 77-6693

Receptors, Hormone (cont'd)

- Progesterone
 - Mammary Neoplasms, Experimental, 77-6692
- Prolactin
 - Mammary Neoplasms, Experimental, 77-6692

Rectal Neoplasms

- Adenocarcinoma
 - 2-Benzimidazolecarbamic Acid, Methyl Ester 77-6786
 - Guanidine, Dodecyl-, Acetate, 77-6786
- 2-Benzimidazolecarbamic Acid, Methyl Ester
 - Transplacental Carcinogenesis, 77-6786
- Guanidine, Dodecyl-, Acetate
 - Transplacental Carcinogenesis, 77-6786

Respiratory System

- Anabesine, 1-Nitroso-
 - Carcinogenic Potential, Hamster, 77-6706

Respiratory Tract Neoplasms

- 1-Butanamine, *N*-Butyl-*N*-nitroso-
 - Transplacental Carcinogenesis, 77-6776
- Diethylamine, *N*-Nitroso-
 - Review, 77-6629
 - Transplacental Carcinogenesis, 77-6776
- Dimethylamine, *N*-Nitroso-
 - Review, 77-6629
 - Transplacental Carcinogenesis, 77-6776
- Dipropylamine, *N*-Nitroso-
 - Transplacental Carcinogenesis, 77-6776
- Hydrazine
 - Review, 77-6629
- Nicotine, 1'-Nitroso-1'-demethyl-
 - Histological Study, Hamster, 77-6706
- Papilloma
 - Ultrastructural Study, 77-7097
- Piperidine, 1-Nitroso-
 - Histological Study, Hamster, 77-6706
 - Transplacental Carcinogenesis, 77-6759
- Polycyclic Hydrocarbons
 - Review, 77-6629
 - Transplacental Carcinogenesis
 - Mouse, 77-6629
- Urea, Ethyl Nitroso-
 - Review, 77-6629

Reticuloendothelial System

- Neoplasms, Experimental
 - Listeria monocytogenes*, 77-7047
- Sarcoma
 - Immunity, Cellular, 77-7047

Reticulosarcoma

- see Sarcoma, Reticulum Cell

Retinol, Hexadecanoate

- Benz(a)anthracene, 7,12-Dimethyl-
 - Ultrastructural Study, Epidermis, Mouse, 77-6688
- Skin Neoplasms
 - Benz(a)anthracene, 7,12-Dimethyl-, 77-6688
 - Precancerous Conditions, 77-6688

Reverse Transcriptase

- DNA Replication
 - Isolation and Characterization, 77-6951
- Erythroleukemia
 - Virus, Friend Murine Leukemia, 77-6956
- Hodgkin's Disease
 - Virus, Rauscher Murine Leukemia, 77-6953
- Lymphosarcoma

Reverse Transcriptase (cont'd)

- Virus, C-Type RNA Tumor, 77-6975
- Oncogenic Viruses
 - Ribonuclease, 77-6951
- Virus, Avian Leukosis
 - DNA Replication, 77-6916
 - Nucleotide Incorporation, 77-6916
 - Temperature Sensitive Mutants, 77-6916
- Virus, Avian Sarcoma
 - DNA Replication, 77-6916
 - Nucleotide Incorporation, 77-6916
 - Temperature Sensitive Mutants, 77-6916
- Virus, Baboon
 - Isolation and Characterization, 77-7006
- Virus, Friend Murine Leukemia
 - Erythropoiesis, 77-6956
 - Methane, Sulfinylbis-, 77-6956
 - Uridine, 5-Bromo-2'-deoxy-, 77-6956
- Virus, Rauscher Murine Leukemia
 - DNA, 77-6954
 - DNA Replication, 77-6951
 - Isolation and Characterization, 77-6951
 - Ribonuclease, 77-6951
 - Streptovaricins, 77-6955
 - Virus, C-Type RNA Tumor, 77-6954

Rhabdomyosarcoma

- IgM
 - Transplantation Immunology, 77-7036
- Lymphocytes
 - Transplantation Immunology, 77-7036

Riboflavine

- Esophageal Neoplasms
 - Carcinogen, Chemical, 77-6666

Ribonuclease

- Oncogenic Viruses
 - Reverse Transcriptase, 77-6951
- Virus, Rauscher Murine Leukemia
 - Reverse Transcriptase, 77-6951

Ribosomes

- Aflatoxin B1
 - Liver, 77-6668

RNA, Messenger

- Acetamide, Thio-
 - Metabolism, 77-6788
- Dimethylamine, *N*-Nitroso-
 - Metabolism, 77-6788
- Liver Neoplasms
 - Acetamide, Thio-, 77-6788
 - Dimethylamine, *N*-Nitroso-, 77-6788

RNA Replication

- Arsenious Acid, Sodium Salt
 - Escherichia coli*, 77-6808
- Ethyl Alcohol
 - HeLa Cells, Review, 77-6610
- Virus, Friend Murine Leukemia
 - Translational Inhibitor, Isolation and Characterization, 77-7188
- Virus, Polyoma
 - Actinomycin D, 77-6978
 - α -Amanitine, 77-6978
 - Fibroblasts, 77-6978
 - Temperature Sensitive Mutants, 77-6977

RNA, Ribosomal

- Acetohydroxamic Acid, *N*-Fluoren-2-yl-

RNA, Ribosomal (cont'd)

- Dose-Response Study, 77-6832
- Hepatectomy, 77-6832
- Liver, Rat, 77-6832
- Poly A, 77-6832
- Barbituric Acid, 5-Ethyl-5-phenyl-
Liver, Rat, 77-6678
- Cholanthrene, 3-Methyl-
Liver, Rat, 77-6678

RNA, Transfer, Methyltransferases

- Butyric Acid, 2-Amino-4-(ethylthio)-
Adenine, 77-6789
- Barbituric Acid, 5-Ethyl-5-phenyl-, 77-6789
- Liver, Rat, 77-6789

RNA, Viral

- Chondrosarcoma
Cells, Cultured, 77-6990
- Virus, C-Type RNA Tumor, 77-6990
- Hodgkin's Disease
Spleen, 77-6952
- Leukemia
Spleen, 77-6952
- Multiple Myeloma
Spleen, 77-6952
- Virus, Adeno 2
DNA-RNA Hybridization, 77-6987
- R-Loop Formation, 77-6987
- Ultrastructural Study, 77-6987
- Virus, Avian Sarcoma
Viral Proteins, 77-6922
- Virus, C-Type RNA Tumor
Carrier Proteins, 77-6932
- Virus, D-Type RNA Tumor
Isolation and Characterization, Review, 77-6638
- Virus, Feline Leukemia
Cells, Cultured, 77-6935
- Virus, Murine Mammary Tumor
Hepatoma, 77-6942
- Virus, Rous Sarcoma
Carrier Proteins, 77-6932
- DNA Nucleotidyltransferases, 77-6924
- DNA Replication, 77-6924
- DNA-RNA Hybridization, 77-6924
- Phosphoproteins, 77-6932

o 10-9359

- Skin Neoplasms
Benz(a)anthracene, 7,12-Dimethyl-, 77-6685
- Neoplasm Regression, 77-6685
- Papilloma, 77-6685

otenone

- Mammary Neoplasms, Experimental
Adenofibroma, 77-6677

U 16117

- see Estradiol, Ethinyl-11 α -methoxy-

ubratoxin B

- Aflatoxin B1
Body Weight, 77-6672
- LD 50, 77-6672
- LD 50
Age Factors, Mouse, 77-6672

iliva

- Virus, Feline Leukemia
Horizontal Transmission, Review, 77-6640

Salmonella typhimurium

- Acetamide, *N*-Fluoren-2-yl-
Mutagenic Activity, 77-6802
- Acrylamide, 2-(2-Furyl)-3-(5-nitro-2-furyl)-
Mutagenic Activity, 77-6802
- Aniline, *N,N*-Dimethyl-*p*-phenylazo-
Mutagenic Activity, 77-6802
- 2-Anthracenamide
Mutagenic Activity, 77-6795
- Benz(a)anthracene
Mutagenic Activity, 77-6721
- Benz(a)anthracene, 7,12-Dimethyl-
Mutagenic Activity, 77-6795
- 1,2-Benzisothiazolin-3-one, 1,1-Dioxide, Sodium Salt
Mutagenic Activity, 77-6682
- Benzo(a)pyrene
Mutagenic Activity, 77-6721, 77-6795, 77-6802
77-6830
- 2-Biphenylamine
Mutagenic Activity, 77-6795, 77-6840
- Carbamic Acid, *N*-Methyl-*N*-nitroso-, Ethyl Ester
Mutagenic Activity, 77-6795
- Carbidiium
Mutagenic Activity, 77-6828
- Chloramphenicol
DNA, 77-6829
- Mutagenic Activity, 77-6829
- Diethylamine, 2,2'-Dichloro-*N*-methyl-
Mutagenic Activity, 77-6795
- Ethidium Bromide
Mutagenic Activity, 77-6828
- Fluoren-2-amine
Mutagenic Activity, 77-6795, 77-6831
- Formamide, *N*-(4-(5-Nitro-2-furyl)-2-thiazolyl)-
Mutagenic Activity, 77-6840
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
DNA Repair, 77-6749
- Mutagenic Activity, 77-6749, 77-6795
- Methanesulfonic Acid, Ethyl Ester
Mutagenic Activity, 77-6795
- Methanesulfonic Acid, Methyl Ester
Mutagenic Activity, 77-6795
- Norharman
Mutagenic Activity, 77-6802
- 1,2-Oxathiolane, 2,2-Dioxide
Mutagenic Activity, 77-6795
- Piperidine, 1-Nitroso-
Mutagenic Activity, 77-6761
- Polycyclic Hydrocarbons
Mutagenic Activity, 77-6830
- Proline, 4-Hydroxy-1-nitroso-
Mutagenic Activity, 77-6761
- Proline, 1-Nitroso-
Mutagenic Activity, 77-6761
- Prothidium
Mutagenic Activity, 77-6828
- Pyrene
Mutagenic Activity, 77-6802
- 9*H*-Pyrid(3,4-*b*)indole, 1-Methyl-
Mutagenic Activity, 77-6802
- 5*H*-Pyrido(4,3-*b*)indole, 3-Amino-1,4-dimethyl-
Mutagenic Activity, 77-6802
- 5*H*-Pyrido(4,3-*b*)indole, 3-Amino-1-methyl-
Mutagenic Activity, 77-6802
- Pyrrolidine, 3-Hydroxy-1-nitroso-
Mutagenic Activity, 77-6761
- Pyrrolidine, 1-Nitroso-

***Salmonella typhimurium* (cont'd)**

- Mutagenic Activity, 77-6761
- Quinoline, 4-Nitro-, 1-Oxide
 - DNA Repair, 77-6749
 - Mutagenic Activity, 77-6749, 77-6795, 77-6802
- 4-Stilbenamine, *N,N*-Dimethyl-
 - Mutagenic Activity, 77-6802
- Stilbene
 - Mutagenic Activity, 77-6802
- Streptozotocin
 - Mutagenic Activity, 77-6795
- 12-*O*-Tetradecanoylphorbol-13-acetate
 - DNA Repair, 77-6749
 - Mutagenic Activity, 77-6749
- o*-Toluenesulfonamide
 - Mutagenic Activity, 77-6682
- o*-Toluidine, 4-(*o*-Tolylazo)-
 - Mutagenic Activity, 77-6795
- Urea, Methyl Nitroso-
 - Mutagenic Activity, 77-6795

Sarcoma

- Acetic Acid, Vinyl Ester
 - Ethylene, Chloro- Polymer, 77-6910
- Cell Membrane
 - DNA Replication, 77-7189
- Cholanthrene, 3-Methyl-
 - Antigens, 77-7086
 - Hybrid Cells, 77-7087
 - Immunity, 77-7086
- Cytosine Nucleotides
 - DNA Replication, 77-7189
- Deoxyribonuclease
 - DNA Replication, 77-7189
- Dog
 - Ultrastructural Study, 77-7117
- Ethylene, Chloro- Polymer
 - Antilymphocyte Serum, 77-7035
 - Azathioprine, 77-7035
 - Histocompatibility Antigens, 77-7035
 - Immunosuppression, 77-7035
- Foreign Bodies
 - Histocompatibility Antigens, 77-7035
 - Immunosuppression, 77-7035
- Guanosine Triphosphate
 - DNA Replication, 77-7189
- Hybrid Cells
 - Chromosomes, 77-7087
 - Histocompatibility Antigens, 77-7087
- Immunity, Cellular
 - Reticuloendothelial System, 77-7047
- Leukemia
 - Virus, Avian Erythroblastosis, 77-6915
- Nasopharyngeal Neoplasms
 - Epidemiology, 77-7156
- Neoplasm Transplantation
 - Dog, 77-7117
- Neoplasms, Experimental
 - Cholanthrene, 3-Methyl-, 77-7047
- Nitrous Acid, Sodium Salt
 - Guanidine, Methyl-, 77-6714
- Pleural Neoplasms
 - Fiber Glass, 77-6911
- 1*H*-Pyrrole-2,5-dione, 1-Ethyl-
 - DNA Replication, 77-7189
- Uracil Nucleotides
 - DNA Replication, 77-7189
- Virus, Herpes Simplex 2

Sarcoma (cont'd)

- Neoplasm Transplantation, 77-7003
- Virus, Rous Sarcoma
 - DNA Replication, 77-7189
 - Temperature Sensitive Mutants, 77-6918
 - Virus Subgroup, 77-6918
- Virus, SV40
 - Histocompatibility Antigens, 77-7045

Sarcoma, Mast Cell

- Antibodies, Neoplasm
 - Ascitic Fluid, 77-7049
- Antigens, Neoplasm
 - Immunity, Cellular, 77-7049
- Chromium Release Assay
 - Antibodies, Neoplasm, 77-7049
- Growth
 - Antigens, Neoplasm, 77-7049
 - Immunoglobulins, Surface, 77-7049
- Immunity, Cellular
 - Chromium Release Assay, 77-7049

Sarcoma, Osteogenic

- Alpha Particles
 - Epidemiology, Review, 77-6630
- Antigens
 - Immune Serums, 77-7031
- Bone Neoplasms
 - Strontium Radioisotopes, 77-6884
- Immune Serums
 - Antibodies, 77-7031
- Radioisotopes
 - Transplantation, Homologous, 77-7039
- Transplantation, Homologous
 - Immune Response, 77-7039

Sarcoma, Reticulum Cell

- Hypersensitivity, Delayed
 - Immune Response, 77-7032
- Immunoglobulins
 - Immune Response, 77-7032
- Immunosuppression
 - Diagnosis and Prognosis, 77-7032
- Lymphopenia
 - Immune Response, 77-7032
- Streptodornase and Streptokinase
 - Immune Response, 77-7032
- Virus, Epstein-Barr
 - Antigen-Antibody Reactions, 77-6994

Sarcoma, Yoshida

- Brain Neoplasms
 - Neoplasm Metastasis, 77-7136
- Hepatoma
 - Neoplasm Circulating Cells, 77-7136
- Neoplasm Circulating Cells
 - Transcerebral Passage, 77-7136

Seclazone

- Cholanthrene, 3-Methyl-
 - Aryl Hydrocarbon Hydroxylases, 77-6755
- Skin Neoplasms
 - Cholanthrene, 3-Methyl-, 77-6755

Selenious Acid, Disodium Salt

- Arsenious Acid, Sodium Salt
 - Cell Survival, 77-6810

Selenium

- Arsenic Acid, Sodium Salt
 - Excretion, Rat, 77-6809

Selenium (cont'd)

Tissue Distribution, Rat, 77-6809

Seminoma

see Disgerminoma

Serum Albumin

Cadmium Sulfate

Blood Chemical Analysis, Rat, 77-6812

Cell Transformation, Neoplastic

Solid Tumors, Review, 77-6651

Lymphocytes

Cell Movement, 77-7080

Chemotaxis, 77-7080

Nickel Sulfide

Dissolution Kinetics, 77-6807

Serum Globulins

Cadmium Sulfate

Blood Chemical Analysis, Rat, 77-6812

Cell Transformation, Neoplastic

Solid Tumors, Review, 77-6651

Skin Chromosomes

Chondrosarcoma

Cells, Cultured, 77-6990

Skin Neoplasms

Benz(a)anthracene, 7,12-Dimethyl-

Benzo(b)triphenylene, 77-6689

Precancerous Conditions, 77-6688

Retinol, Hexadecanoate, 77-6688

Ro 10-9359, 77-6685

Benzo(a)pyrene, 7,8-Dihydro-7,8-dihydroxy-

Carcinogenic Activity, Mouse, 77-6742

12-*O*-Tetradecanoylphorbol-13-acetate, 77-6742

Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-

tetrahydro-

Carcinogenic Activity, Mouse, 77-6742

12-*O*-Tetradecanoylphorbol-13-acetate, 77-6742

Benzo(a)pyrene 9,10-Oxide

Carcinogenic Activity, Mouse, 77-6742

12-*O*-Tetradecanoylphorbol-13-acetate, 77-6742

Benzo(a)pyrene 11,12-Oxide

Carcinogenic Activity, Mouse, 77-6742

12-*O*-Tetradecanoylphorbol-13-acetate, 77-6742

Carcinoma, Basal Cell

Case Report, 77-7098

Epidemiology, 77-7172

Neoplasm Metastasis, 77-7098

Sex Factors, 77-7172

Carcinoma, Epidermoid

Epidemiology, 77-7172

Sex Factors, 77-7172

Ultraviolet Rays, 77-6905

Cholanthrene, 3-Methyl-

Dexamethasone, 77-6755

Indole-3-acetic acid, 1-(*p*-Chlorobenzoyl)-5-

methoxy-2-methyl-, 77-6755

3,5-Pyrazolidinedione, 4-Butyl-1-(*p*-hydroxyphenyl)-

2-phenyl-, 77-6755

Seclazone, 77-6755

Dipropylamine, 2,2'-Diacetoxy-*N*-nitroso-

Hamster, 77-6762

Epidemiology

Poland, 77-7172

Sex Factors, 77-7172

Fibrosarcoma

Ultrastructural Study, 77-7099

Hemangioma

Skin Neoplasms (cont'd)

Epidemiology, Review, 77-6656

Melanoma

Epidemiology, 77-6636

Epidemiology, Review, 77-6656

Genetics, 77-6636

Pigmentation, 77-6636

Review, 77-6636

Ultraviolet Rays, 77-6636

Neoplasms, Multiple Primary

Animal Model, Review, 77-6655

Precancerous Conditions, 77-6655

Paget's Disease, Extra-Mammary

Epidemiology, Review, 77-6656

Papilloma

Benz(a)anthracene, 7,12-Dimethyl-, 77-6685

Ro 10-9359, 77-6685

Precancerous Conditions

Diagnosis, Review, 77-6656

2-Propanol, 1,1'-Iminodi-*N*-nitroso-

Hamster, 77-6762

Retinol, Hexadecanoate

Precancerous Conditions, 77-6688

Ro 10-9359

Neoplasm Regression, 77-6685

Smoking

Mouse, 77-6703

12-*O*-Tetradecanoylphorbol-13-acetate

Carcinogenic Activity, Mouse, 77-6742

Ultraviolet Rays

Carcinogenic Potential, 77-6905

Epidemiology, Review, 77-6656

Smoking

Asbestos

Co-carcinogenic Activity, Review, 77-6627

Co-carcinogenic Effect, 77-7173

Epidemiology, 77-7173

Epidemiology, Review, 77-6628

Benzo(a)pyrene

Condensate, 77-6701

Bronchi

Glycoproteins, 77-7092

Carcinogen, Chemical

Benz(e)acephenanthrylene, 77-6626

Benzo(a)pyrene, 77-6626

Benzo(j)fluoranthene, 77-6626

Chrysene, 5-Methyl-, 77-6626

Dibenz(a,h)anthracene, 77-6626

Dibenz(a,j)acridine, 77-6626

Dibenzo(b,def)chrysene, 77-6626

Isolation and Characterization, 77-6626

Carcinogenic Potential

Ultrastructural Study, Vero Cells, 77-6700

Cell Differentiation

Lung, Chicken, 77-6704

Mesenchyma, 77-6704

Cell Transformation, Neoplastic

Animal Model, Review, 77-6602

Epidemiology

Statistical Analysis, 77-7148

Glucosephosphate Dehydrogenase

Histochemical Study, Vero Cells, 77-6700

Hodgkin's Disease

Epidemiology, 77-7154

Isoenzymes

Cells, Cultured, 77-6700

Lactate Dehydrogenase Isoenzymes

Smoking (cont'd)

- Histochemical Study, Vero Cells, 77-6700
- Liver
 - Cat, 77-6705
 - Metabolism, 77-6705
 - Rat, 77-6705
- Lung Neoplasms
 - Aryl Hydrocarbon Hydroxylases, 77-6757
 - Carcinoma, Epidermoid, 77-6663
 - Epidemiology, USSR, 77-6664
 - Mouse, 77-6703
- Lymphocytes
 - Aryl Hydrocarbon Hydroxylases, 77-6757
- Macrophages
 - Aryl Hydrocarbon Hydroxylases, 77-6757
- Malate Dehydrogenase
 - Histochemical Study, Vero Cells, 77-6700
- Mitosis
 - Mesenchyma, 77-6704
- Neoplasm Metastasis
 - Epidemiology, 77-7148
- Nicotine
 - Carboxyhemoglobin, 77-6758
 - Condensate, 77-6701
 - Metabolism, 77-6705
- Phenol
 - Condensate, 77-6701
- Rat
 - Dosimetry, 77-6817
- Skin Neoplasms
 - Mouse, 77-6703
- Stearic Acid
 - Condensate, 77-6701
- Sodium Arsenate
 - see Arsenic Acid, Sodium Salt
- Sodium Arsenite
 - see Arsenious Acid, Sodium Salt
- Soil Pollutants
 - Benzo(a)pyrene
 - Hungary, 77-6737
- Somatotropin
 - Mammary Neoplasms, Experimental
 - Estradiol, Ethinyl-11 α -methoxy-, 77-6695
- Spherocytosis, Hereditary
 - Benzoic Acid, *p*-Mercuri-
 - Phosphorylation, 77-7185
 - Erythrocytes
 - Phosphorylation, 77-7185
 - Proteins
 - Phosphorylation, 77-7185
 - 1*H*-Pyrrole-2,5-dione, 1-Ethyl-
 - Phosphorylation, 77-7185
 - Surface Properties
 - Phosphorylation, 77-7185
- Spinal Cord
 - Radiation, Ionizing
 - Nerve Degeneration, 77-6901
- Spinal Cord Neoplasms
 - Radiation, Ionizing
 - Histological Study, Rat, 77-6901
 - Neurilemmoma, 77-6901
 - Precancerous Conditions, 77-6901

Spleen

- Hodgkin's Disease
 - RNA, Viral, 77-6952
- Leukemia
 - RNA, Viral, 77-6952
- Leukemia, Hairy Cell
 - Acid Phosphatase, 77-7134
 - Pyrophosphatases, 77-7134
- Multiple Myeloma
 - RNA, Viral, 77-6952
- Virus, Murine Leukemia
 - Virus Replication, 77-6945
- Stearic Acid
 - Smoking
 - Condensate, 77-6701
- Steroids
 - Hepatoma
 - Review, 77-6622
- 4-Stilbenamine, *N,N*-Dimethyl-*Salmonella typhimurium*
 - Mutagenic Activity, 77-6802
- Stilbene
 - Salmonella typhimurium*
 - Mutagenic Activity, 77-6802
- 4,4'-Stilbenediol, α,α' -Diethyl-
 - Animal Feed
 - Toxicology, 77-6868
 - Cell Transformation, Neoplastic
 - Animal Model, Review, 77-6602
 - Gynecologic Neoplasms
 - Age Factors, 77-7157
 - Epidemiology, 77-7157
 - Precancerous Conditions, 77-6870
 - Precancerous Conditions, Review, 77-6615
 - Transplacental Carcinogenesis, 77-6870, 77-7157
 - Transplacental Carcinogenesis, Review, 77-6615
 - Kidney Neoplasms
 - MSH, 77-6872
 - Lung Neoplasms
 - Adenoma, 77-6869
 - Mouse, 77-6869
 - Transplacental Carcinogenesis, 77-6869
 - MSH
 - Serum/Pituitary Levels, 77-6872
 - Thymus Gland
 - Mouse, 77-6871
 - Uterine Neoplasms
 - Adenocarcinoma, 77-6867
 - Histological Study, 77-6867
 - Uterus
 - Mouse, 77-6871
 - Vagina
 - Mouse, 77-6871
- Stomach Neoplasms
 - Adenocarcinoma
 - Guanidine, 1-Ethyl-3-nitro-1-nitroso-, 77-6710
 - 77-6711
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6710
 - 77-6711
 - Adenoma
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6713
 - Asbestos
 - Epidemiology, 77-6914
 - Benzo(a)pyrene

Stomach Neoplasms (cont'd)

- Benzene, (2-Isothiocyantoethyl)-, 77-6683
- Benzene, (2-Isothiocyantomethyl)-, 77-6683
- Carcinoma
 - Epidemiology, 77-7103
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6713
 - Urea, Methyl Nitroso-, 77-7142
- Carcinoma, Epidermoid
 - Guanidine, 1-Ethyl-3-nitro-1-nitroso-, 77-6710
 - Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-6710
- Epidemiology
 - Chile, 77-7167
 - Diagnosis and Prognosis, 77-7166
 - USSR, 77-7165, 77-7166
- Esophageal Neoplasms
 - Neoplasms, Multiple Primary, 77-7104
- Guanidine, 1-Ethyl-3-nitro-1-nitroso-
 - Histological Study, Rat, 77-6711
 - Neoplasm Metastasis, 77-6711
 - Precancerous Conditions, 77-6711
 - Ultrastructural Study, Rat, 77-6710
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Histological Study, Rat, 77-6711
 - Lysosomes, 77-6713
 - Neoplasm Metastasis, 77-6711
 - Precancerous Conditions, 77-6711, 77-6713
 - Ultrastructural Study, Rat, 77-6710, 77-6713
- Mammary Neoplasms, Experimental
 - Benzene, (2-Isothiocyantoethyl)-, 77-6683
 - Benzene, (2-Isothiocyantomethyl)-, 77-6683
- Neoplasms, Multiple Primary
 - Precancerous Conditions, 77-7104
- Nitroso Compounds
 - Epidemiology, Review, 77-6611
- Urea, Methyl Nitroso-
 - Histological Study, Rat, 77-7142

Streptovaricins

- Virus, Rauscher Murine Leukemia
 - Reverse Transcriptase, 77-6955
 - Splenomegaly, 77-6955
 - Virus Replication, 77-6955

Streptozotocin

- 2,3-Butanediol, 1,4-Dimercapto-
 - Guanyl Cyclase, 77-6779
- Guanosine Cyclic 3',5' Monophosphate
 - Liver, Renal Cortex, Dog, 77-6779
- Guanyl Cyclase
 - Cations, Divalent, 77-6779
 - Enzyme Activation, Rat, 77-6781
- Hepatoma
 - Histological Study, 77-6673
- Kidney
 - Guanyl Cyclase, 77-6779
- Liver Neoplasms
 - Adenoma, 77-6673
 - Histological Study, 77-6673
- Maleic Acid
 - Glutathione, 77-6779
 - Guanyl Cyclase, 77-6779
- Maleimide, *N*-Ethyl-
 - Guanyl Cyclase, 77-6779
- Salmonella typhimurium*
 - Mutagenic Activity, 77-6795

Stress

- Virus, Polyoma
 - Immune Response, 77-6908

Stress (cont'd)

- Ultrasonics, 77-6908

Strontium Radioisotopes

- Bone Neoplasms
 - Chondrosarcoma, 77-6884
 - Fibrosarcoma, 77-6884
 - Iodine Radioisotopes, 77-6884
 - Sarcoma, Osteogenic, 77-6884
 - Thyroidectomy, 77-6884

Submandibular Gland

- Benz(a)anthracene, 7,12-Dimethyl-
 - Cell Transformation, Neoplastic, 77-6686
- Cells, Cultured
 - Cell Transformation, Neoplastic, 77-6686

Sulfanilamide, *N*-2-Thiazolyl-

- Acetic Acid, Lead Salt
 - Co-carcinogenic Activity, 77-6805
- Kidney Neoplasms
 - Acetic Acid, Lead Salt, 77-6805

Sulfonic Acid, α -Alkene-

- Adrenal Gland Neoplasms
 - Dose-Response Study, Rat, 77-6791
- Pancreatic Neoplasms
 - Dose-Response Study, Rat, 77-6791
 - Islet Cell Tumor, 77-6791
- Thyroid Neoplasms
 - Dose-Response Study, Rat, 77-6791

Sulfuric Acid, Dimethyl Ester

- DNA Repair
 - Cells, Cultured, 77-6792

Synestrol

- see Dienestrol

Teratocarcinoma

- see Teratoid Tumor

Teratogens

- Abortion
 - Epidemiology, Review, 77-6625
 - Monitoring, Environmental, Review, 77-6625

Teratoid Tumor

- Cell Aggregation
 - Plasminogen, 77-7147
- Cell Differentiation
 - Plasminogen, 77-7147
- Cells, Cultured
 - Plasminogen, 77-7147
- Dibutyl Cyclic AMP
 - Plasminogen, 77-7147
- FSH
 - Gonadotropins, Pituitary, 77-6806
- Guanidine, 1-Methyl-3-nitro-1-nitroso-
 - Cell Differentiation, 77-7044
 - Immunity, Passive, 77-7044
 - Transplantation Immunology, 77-7044
- LH
 - Gonadotropins, Pituitary, 77-6806
- Radiation, Ionizing
 - Cell Differentiation, 77-7044
 - Immunity, Passive, 77-7044
- Testicular Neoplasms
 - Copper Sulfate Pentahydrate, 77-6806
- Theophylline
 - Plasminogen, 77-7147
- Toxins

Teratoid Tumor (cont'd)
Plasminogen, 77-7147

Teratoma
see Teratoid Tumor

Testicular Neoplasms
Copper Sulfate Pentahydrate
Gonadotropins, Pituitary, 77-6806
Disgerminoma
Copper Sulfate Pentahydrate, 77-6806
Epidemiology, 77-7161
Occupational Hazard
Epidemiology, 77-7161
Socioeconomic Factors
Epidemiology, 77-7161
Teratoid Tumor
Copper Sulfate Pentahydrate, 77-6806

Testosterone
Animal Feed
Toxicology, 77-6868
Breast Neoplasms
Diet, 77-7162
Ultrastructural Study
Prostate, 77-7118

Testosterone, Propionate
Prostatic Neoplasms
Adenocarcinoma, 77-6876

Testosterone, Propionate, *p*-Hexaphenyl-
Prostatic Neoplasms
Hyperplasia, 77-6877
Metabolism, Rat, 77-6877

12-*O*-Tetradecanoylphorbol-13-acetate
Adenosine Cyclic 3',5' Monophosphate
Epidermis, Mouse, 77-6747
Benz(a)anthracene, 7,12-Dimethyl-
Hair, Mouse Tail, 77-6743
Carboxy-Lyases
Cell Transformation, Neoplastic, 77-6744
Embryo, Hamster, 77-6744
Enzymatic Activity, 77-6744
Cell Differentiation
Cell Transformation, Neoplastic, 77-6745
Cell Membrane
Cell Cycle Kinetics, 77-6750
Cells, Cultured
Cell Differentiation, 77-6748
DNA Replication
Cell Transformation, Neoplastic, 77-6744
Embryo, Hamster, 77-6744
Epinephrine
Adenosine Cyclic 3',5' Monophosphate, 77-6747
Isoproterenol
Adenosine Cyclic 3',5' Monophosphate, 77-6747
Lipids
Cell Differentiation, 77-6748
Papilloma
Precancerous Conditions, 77-6743
Salmonella typhimurium
DNA Repair, 77-6749
Mutagenic Activity, 77-6749
Skin Neoplasms
Benzo(a)pyrene, 7,8-Dihydro-7,8-dihydroxy-
77-6742
Benzo(a)pyrene, 7,8-Dihydroxy-9,10-oxy-7,8,9,10-
tetrahydro-, 77-6742

12-*O*-Tetradecanoylphorbol-13-acetate (cont'd)
Benzo(a)pyrene 9,10-Oxide, 77-6742
Benzo(a)pyrene 11,12-Oxide, 77-6742
Carcinogenic Activity, Mouse, 77-6742
Ultraviolet Rays
Ouabain Resistance, 77-6746
Thioguanine Resistance, 77-6746

Theophylline
Breast Neoplasms
Dibutyl Cyclic AMP, 77-6865
DNA Replication, 77-6865
Teratoid Tumor
Plasminogen, 77-7147

Thiazol, 2-Formylamine-4-(5-nitro-2-furyl)-
Bladder Neoplasms
Dog, 77-6840

Thiocyanic Acid, Phenylmethyl Ester
Mammary Neoplasms, Experimental
Benz(a)anthracene, 7,12-Dimethyl-, 77-6683

Thorium Dioxide
Liver Neoplasms
Occupational Hazard, 77-6622

Thymidine
Mammary Neoplasms, Experimental
Estrus, 77-6702

Thymidine Kinase
Lung Neoplasms
Isolation and Characterization, 77-7195
Radiation
Lymphocytes, 77-6898

Thymoma
Agammaglobulinemia
Lymphocytes, 77-7064
Immune Response
Review, 77-6649
T-Lymphocytes
Transplantation Immunology, 77-7068
Virus, Rauscher Murine Leukemia
Transplantation Immunology, 77-7068

Thymus Gland
4,4'-Stilbenediol, α,α' -Diethyl-
Mouse, 77-6871
Virus, Murine Leukemia
Mouse, Nude, 77-6945
Virus Replication, 77-6945
Virus, Murine Mammary Tumor
Cell Transformation, Neoplastic, 77-7066

Thymus Neoplasms
Dimethylamine, *N*-Nitroso-
Carcinogenic Potential, Rat, 77-6769
Leukemia, Radiation-Induced
Virus, Murine Leukemia, 77-6962
Lymphoma
Urea, Methyl Nitroso-, 77-7142
Urea, Methyl Nitroso-
Histological Study, Rat, 77-7142
Virus, Murine Leukemia
Isolation and Characterization, 77-6965

Thyroid Hormones
Thyroid Neoplasms
Thyrotropin, 77-6635

Thyroid Neoplasms

- Adenoma
 - Radiation, Ionizing, 77-6635, 77-6889
 - Radioactive Fallout, 77-6882
 - Radiotherapy, 77-6632
- Breast Neoplasms
 - Epidemiology, 77-6633
- Carcinoma
 - Chromosome Aberrations, 77-6634
 - Diagnosis and Prognosis, 77-6634
 - Epidemiology, 77-6633
 - Goiter, Exophthalmic, 77-6633
 - Radiation, Ionizing, 77-6633, 77-6634, 77-6635, 77-6885, 77-6889, 77-6890, 77-6891
 - Review, 77-6633
- Chromosome Aberrations
 - Thyrotropin, 77-6634
- Goiter, Exophthalmic
 - Radiotherapy, 77-6632
- Hyperparathyroidism
 - Radiotherapy, 77-6632
- Iodine Radioisotopes
 - Epidemiology, Review, 77-6632
 - Histological Study, Review, 77-6632
 - Radioactive Fallout, 77-6882
- Radiation, Ionizing
 - Dose-Response Study, 77-6888
 - Epidemiology, 77-6885, 77-6887, 77-6888, 77-6890
 - Histological Study, 77-6889
- Radioactive Fallout
 - Dose-Response Study, 77-6882
 - Epidemiology, Marshall Islands, 77-6882
- Sulfonic Acid, α -Alkene-
 - Dose-Response Study, Rat, 77-6791
- Thyrotropin
 - Thyroid Hormones, 77-6635
- Thyrotropin
 - Thyroid Neoplasms
 - Chromosome Aberrations, 77-6634
 - Thyroid Hormones, 77-6635

Tibia

- Bone Neoplasms
 - Case Report, 77-7100
 - Histological Study, 77-7100
 - Ultrastructural Study, 77-7100

Tissue Culture

- Pancreatic Ducts
 - Nucleic Acids, 77-7107
 - Proteins, 77-7107
 - Ultrastructural Study, 77-7107

Tobacco

- Nitrous Acid
 - Nicotine, 77-6707
 - Nicotine, 1'-Demethyl-, 77-6707

Tocopherol

- Nitrous Acid, Sodium Salt
 - Antipyrone, 4-(Dimethylamino)-, 77-6717

Tocopherol

- Nitrous Acid, Sodium Salt
 - Antipyrone, 4-(Dimethylamino)-, 77-6717

Tocopherolquinone

- Nitrous Acid, Sodium Salt
 - Antipyrone, 4-(Dimethylamino)-, 77-6717

Toluene, 2,4-Dinitro-Ozone

- Mutagenic Activity, 77-6798
- Water Pollutants
 - Ozone, 77-6798

o-Toluenesulfonamide

- Salmonella typhimurium*
 - Mutagenic Activity, 77-6682

o-Toluidine, 4-(*o*-Tolylazo)-

- Antigen-Antibody Reactions
 - Cell Transformation, Neoplastic, 77-6843
- Antigens
 - Binding, Liver, 77-6843
- Benzoic Acid, 2-Amino-3-hydroxy-
 - Antigen-Antibody Reactions, 77-6843
- Cell Survival
 - Liver, Embryo, 77-6844
- Fetal Death
 - Dose-Response Study, Mouse, 77-6844
- Salmonella typhimurium*
 - Mutagenic Activity, 77-6795
- Toxicity
 - Transplacental Effect, 77-6844

Tonsillar Neoplasms

- Virus, Epstein-Barr
 - Seroepidemiology, Review, 77-6643

Torulopsis glabrata

- Neoplasms, Experimental
 - Phagocytosis, 77-7030
 - Transplantation, Homologous, 77-7030

Toxoplasma gondii

- Cholangioma
 - Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-, 77-7061

Hepatoma

- Benzenamine, *N,N*-Dimethyl-4-((3-methylphenyl)azo)-, 77-7061

Tracheal Neoplasms

- Occupational Hazard
 - Epidemiology, 77-7168

Transferases

- Barbituric Acid, 5-Ethyl-5-phenyl-
 - Acetic Acid, (2,3-Dichloro-4-(2-methylenebutyryl)phenoxy)-, 77-6732
- Benzene, 1-Chloro-2,4-dinitro-, 77-6732
- Benzene, 1-(Chloromethyl)-4-nitro-, 77-6732
- Intestine, Rat, 77-6732
- Benzo(a)pyrene
 - Acetic Acid, (2,3-Dichloro-4-(2-methylenebutyryl)phenoxy)-, 77-6732
- Benzene, 1-Chloro-2,4-dinitro-, 77-6732
- Benzene, 1-(Chloromethyl)-4-nitro-, 77-6732
- Intestine, Rat, 77-6732
- Propane, 1,2-Epoxy-3-(*p*-nitrophenoxy)-, 77-6732
- Cholanthrene, 3-Methyl-
 - Acetic Acid, (2,3-Dichloro-4-(2-methylenebutyryl)phenoxy)-, 77-6732
- Benzene, 1-Chloro-2,4-dinitro-, 77-6732
- Benzene, 1-(Chloromethyl)-4-nitro-, 77-6732
- Intestine, Rat, 77-6732
- Propane, 1,2-Epoxy-3-(*p*-nitrophenoxy)-, 77-6732

Transplantation, Heterologous

Liposarcoma

Virus Replication, 77-6976

Lung Neoplasms

Virus Replication, 77-6976

Neuroblastoma

Virus Replication, 77-6976

Transplantation, Homologous

Lymphosarcoma

Neoplasm Metastasis, 77-7125

Neoplasms, Experimental

Antibody Formation, 77-7030

Immunity, Cellular, 77-7030

Lipopolysaccharides, 77-7030

B-Lymphocytes, 77-7030

T-Lymphocytes, 77-7030

Phagocytosis, 77-7030

Plant Agglutinins, 77-7030

Torulopsis glabrata, 77-7030

Sarcoma, Osteogenic

Immune Response, 77-7039

Radioisotopes, 77-7039

Transplantation Immunology

Astrocytoma

IgM, 77-7036

Lymphocytes, 77-7036

Carcinoma

IgM, 77-7036

Lymphocytes, 77-7036

Fibrosarcoma

Benzo(a)pyrene, 77-7068

IgM, 77-7036

Lymphocytes, 77-7036, 77-7068

L Cells

Hybrid Cells, 77-7037

T-Lymphocytes

Plant Agglutinins, 77-7068

Melanoma

IgM, 77-7036

Lymphocytes, 77-7036

Neoplasms, Experimental

Listeria monocytogenes, 77-7047

Nephroblastoma

IgM, 77-7036

Lymphocytes, 77-7036

Rhabdomyosarcoma

IgM, 77-7036

Lymphocytes, 77-7036

Teratoid Tumor

Guanidine, 1-Methyl-3-nitro-1-nitroso-, 77-7044

Thymoma

T-Lymphocytes, 77-7068

Virus, Rauscher Murine Leukemia, 77-7068

Virus, Polyoma

Ultrasonics, 77-6908

Viral Vaccines, 77-6908

Triazole, 3-Amino

Dimethylamine, *N*-Nitroso-

Hepatotoxicity, Rat, 77-6775

Metabolism, Rat, 77-6775

Triton X 100

1-Hexanamine, *N*-Hexyl-

Nitrous Acid, 77-6763

Trypsin

Virus, Rous Sarcoma

Cell Membrane, 77-6917

Tyrosine Aminotransferase

Hepatoma

Concanavalin A, 77-7191

D-Mannopyranoside, α -Methyl-, 77-7191

Ultrasonics

Virus, Polyoma

Stress, 77-6908

Transplantation Immunology, 77-6908

Viral Vaccines, 77-6908

Ultraviolet Rays

Aflatoxin B₁

DNA Repair, 77-6667

DNA Replication, 77-6667

Arsenious Acid, Sodium Salt

DNA Repair, 77-6808

Cells, Cultured

Mutagenic Activity, Hamster, 77-6746

DNA Repair

Cell Survival, 77-6904

Culture Media, 77-6904

DNA, Viral

Thymine Photoproduct, 77-6907

Endonucleases

DNA Repair, 77-6906

Escherichia coli

DNA Repair, 77-6904

Fibrosarcoma

Transplantation Immunology, Review, 77-6637

Haemophilus influenzae

DNA, Viral, 77-6907

Hereditary Diseases

DNA Repair, 77-6903

Lymphocytes

Immune Response, Mouse, Review, 77-6637

Macrophages

Immune Response, Mouse, Review, 77-6637

Melanoma

Transplantation Immunology, Review, 77-6637

Neoplasms, Experimental

Transplantation Immunology, Review, 77-6637

Neoplasms, Multiple Primary

DNA Repair, 77-6903

Nitrosamines

Photolysis, 77-6718

Phorbol

Ouabain Resistance, 77-6746

Thioguanine Resistance, 77-6746

Skin Neoplasms

Carcinogenic Potential, 77-6905

Carcinoma, Epidermoid, 77-6905

Epidemiology, Review, 77-6656

Melanoma, 77-6636

12-*O*-Tetradecanoylphorbol-13-acetate

Ouabain Resistance, 77-6746

Thioguanine Resistance, 77-6746

Virus, Herpes Simplex 1

DNA Repair, 77-7002

Virus Replication, 77-7002

Virus, Rauscher Murine Leukemia

DNA Repair, 77-6858

Virus, Rous Sarcoma

Phosphoproteins, 77-6932

Virus, Shope Rabbit Fibroma

Cell Aggregation, 77-6939

Virus Replication, 77-6939

Virus, Vesicular Stomatitis

Ultraviolet Rays (cont'd)

Virus Replication, 77-6939

Xeroderma Pigmentosum

Caffeine, 77-6903

DNA Repair, 77-6903

Uracil, 5-(Bis(2-chloroethyl)amino)-

Cell Transformation, Neoplastic

Cells, Cultured, Review, 77-6608

Uracil, 5-Fluoro-

Cell Transformation, Neoplastic

Cells, Cultured, Review, 77-6608

DNA Replication

Intestine, Rat, 77-6863

Uracil Nucleotides

Sarcoma

DNA Replication, 77-7189

Urea

Cadmium Sulfate

Blood Chemical Analysis, Rat, 77-6812

Urea, 1,3-Bis(2-chloroethyl)-1-nitroso-

2,3-Butanediol, 1,4-Dimercapto-

Guanyl Cyclase, 77-6779

Cysteine

Guanyl Cyclase, 77-6779

Glutathione

Guanyl Cyclase, 77-6779

Guanosine Cyclic 3',5' Monophosphate

Liver, Renal Cortex, Dog, 77-6779

Guanyl Cyclase

Cations, Divalent, 77-6779

Kidney

Guanyl Cyclase, 77-6779

Maleic Acid

Guanyl Cyclase, 77-6779

1*H*-Pyrrole-2,5-dione, 1-Ethyl-

Guanyl Cyclase, 77-6779

Urea, Butyl-

Nitric Acid, Sodium Salt

Transplacental Carcinogenesis, 77-6778

Urea, 1-Butyl-1-nitroso-

Nervous System Neoplasms

Astrocytoma, 77-6778

Ependymoma, 77-6778

Glioma, 77-6778

Neurilemmoma, 77-6778

Oligodendroglioma, 77-6778

Transplacental Carcinogenesis, 77-6778

Urea, Dodecyl Nitroso-

Guanidine, Dodecyl-, Acetate

Isolation and Characterization, 77-6786

Urea, Ethyl Nitroso-

Chromosome Aberrations

Cells, Cultured, 77-6785

DNA Repair

Cells, Cultured, 77-6792

Glioma

Chromosomes, 77-7137

Lung Neoplasms

Adenocarcinoma, 77-6897

Adenoma, 77-6897

Transplacental Carcinogenesis, 77-6897

Mammary Neoplasms, Experimental

Radiation, Ionizing, 77-6897

Urea, Ethyl Nitroso- (cont'd)

Transplacental Carcinogenesis, 77-6897

Neurilemmoma

Chromosomes, 77-7137

Oligodendroglioma

Chromosomes, 77-7137

Ovarian Neoplasms

Radiation, Ionizing, 77-6897

Transplacental Carcinogenesis, 77-6897

Respiratory Tract Neoplasms

Review, 77-6629

Urea, Hydroxy-

Cell Transformation, Neoplastic

Cells, Cultured, Review, 77-6608

Deoxyribonucleosides

DNA Replication, 77-6787

DNA Repair

Cell Cycle Kinetics, 77-6787

L Cells

DNA Replication, 77-6787

Virus, Herpes Simplex 1

DNA, Viral, 77-7001

Virus Replication, 77-7001, 77-7002

Urea, Methyl Nitroso-

Bladder Neoplasms

Histological Study, 77-6783

Rat, 77-6783

Cell Transformation, Neoplastic

Fetus, Hamster, 77-6784

Colonic Neoplasms

Dietary Fats, 77-6797

DNA Repair

Cells, Cultured, 77-6792

Guanosine Cyclic 3',5' Monophosphate

Liver, Renal Cortex, Dog, 77-6779

Guanyl Cyclase

Cations, Divalent, 77-6779

Enzyme Activation, Rat, 77-6781

Mouth Neoplasms

Hamster, 77-6794

Nervous System Neoplasms

Castration, 77-6780

Dienestrol, 77-6780

Neurilemmoma, 77-6780

Neuroblastoma, 77-6780

Neurofibroma, 77-6780

Neurofibroma

Dienestrol, 77-6780

Neuroglia

Cell Transformation, Neoplastic, 77-6784

Dose-Response Study, Hamster, 77-6784

Nucleotides

Carbamoylation, 77-6782

Salmonella typhimurium

Mutagenic Activity, 77-6795

Stomach Neoplasms

Carcinoma, 77-7142

Histological Study, Rat, 77-7142

Thymus Neoplasms

Histological Study, Rat, 77-7142

Lymphoma, 77-7142

Urea, *N*-Nitroso-*N*-propyl-

Isopropyl Alcohol

Microsomes, Liver, 77-6777

Propyl Alcohol

Microsomes, Liver, 77-6777

Uridine

- Calcium
Biological Transport, 77-7196
- Magnesium
Biological Transport, 77-7196

Uridine, 5-Bromo-2'-deoxy-

- Virus, Friend Murine Leukemia
Reverse Transcriptase, 77-6956

Uridine, 2'-Deoxy-5-fluoro-

- Cell Transformation, Neoplastic
Cells, Cultured, Review, 77-6608
- Virus, Herpes Simplex 1
Virus Replication, 77-7002

Uridine, 2'-Deoxy-5-iodo-

- Virus, Epstein-Barr
Antigens, Viral, 77-6994

Urine

- Virus, Feline Leukemia
Horizontal Transmission, Review, 77-6640

Urticaria Pigmentosa

- Polycythemia Vera
Case Report, 77-7135

Uterine Neoplasms

- Adenocarcinoma
Estradiol, 77-6867
4,4'-Stilbenediol, α,α' -Diethyl-, 77-6867
- Carcinoma
Estrogenic Substances, Conjugated, 77-6874
- Estradiol
Histological Study, 77-6867
Ultrastructural Study, 77-7116
- Estrogenic Substances, Conjugated
Epidemiology, 77-6874
- Estrogens
Epidemiology, 77-6616
4,4'-Stilbenediol, α,α' -Diethyl-
Histological Study, 77-6867

Uterus

- 4,4'-Stilbenediol, α,α' -Diethyl-
Mouse, 77-6871

Vagina

- 4,4'-Stilbenediol, α,α' -Diethyl-
Mouse, 77-6871

Vaginal Neoplasms

- Carcinoma, Epidermoid
Radiation, Ionizing, 77-6892
- Carcinoma In Situ
Radiation, Ionizing, 77-6892
- Dipropylamine, 2,2'-Diacetoxy-*N*-nitroso-
Hamster, 77-6762
Papilloma, 77-6762
- Estradiol
Neonate, Mouse, 77-6875
- Hyperplasia
Estradiol, 77-6875
Progesterone, 77-6875
- Progesterone
Estradiol, 77-6875
Neonate, Mouse, 77-6875
- 2-Propanol, 1,1'-Iminodi-*N*-nitroso-
Hamster, 77-6762
Papilloma, 77-6762

Viral Proteins

- Virus, Avian Leukosis
Tissue Specificity, 77-6992
- Virus, Avian Sarcoma
Cell-Free Synthesis, 77-6922
RNA, Viral, 77-6922
- Virus, B77
Cell Transformation, Neoplastic, 77-6972
Isolation and Characterization, 77-6920, 77-6972
Temperature Sensitive Mutants, 77-6972
- Virus, C-Type RNA Tumor
Genetics, 77-7007
Isolation and Characterization, 77-7007
- Virus, Feline Leukemia
2-Azetidinecarboxylic Acid, 77-6936
Fluoride, Phenylmethylsulfonyl-, 77-6936
Isolation and Characterization, 77-6936
Pactamycin, 77-6936
Peptides, 77-6936
- Virus, Gross Murine Leukemia
Antigens, Viral, 77-6947
Isolation and Characterization, 77-6947
- Virus, Herpes Simplex 1
Cell Transformation, Neoplastic, 77-7000
Concanavalin A, 77-7000
Isolation and Characterization, 77-7000
- Virus, Moloney Murine Sarcoma
Cell Transformation, Neoplastic, 77-6969
Isolation and Characterization, 77-6969
- Virus, Murine Leukemia
Antigenic Determinants, 77-6964
Ascitic Fluid, 77-6961
Immune Serums, 77-6961
Isolation and Characterization, 77-6961
Isolation and Characterization, Mouse, AKR
77-6964
- Virus, Polyoma
Cell Membrane, 77-6979
Cell Transformation, Neoplastic, 77-6979
Temperature Sensitive Mutants, 77-6979
- Virus, Rous Sarcoma
Isolation and Characterization, 77-6926
- Virus, Simian 5
Isolation and Characterization, 77-7009
- Virus, SV40
Cell Transformation, Neoplastic, 77-7027
Phosphorylation, 77-7027
Protein A, Isolation and Characterization, 77-7027
Temperature Sensitive Mutants, 77-7027
Virus Replication, 77-7027

Viral Vaccines

- Virus, Gross Murine Leukemia
Antibody Formation, 77-7043
- Virus, Marek's Disease Herpes
Immune Response, 77-7042
Viral Interference, 77-7042
- Virus, Murine Leukemia
Antibody Formation, 77-7043
- Virus, Polyoma
Transplantation Immunology, 77-6908
Ultrasonics, 77-6908

Virus, Adeno 1

- DNA, Viral
Replication Complex, Isolation and Characteriza-
tion, 77-6986
- Virus, Adeno 5

- Virus, Adeno 1 (cont'd)**
 - DNA Replication, 77-6986
- Virus, Helper**
 - DNA Replication, 77-6986
- Virus, Adeno 2**
 - RNA, Viral
 - DNA-RNA Hybridization, 77-6987
 - R-Loop Formation, 77-6987
 - Ultrastructural Study, 77-6987
- Virus, Adeno 5**
 - Microtubules
 - Binding, 77-6985
 - Brain, Chick, 77-6985
 - Proteins, 77-6985
 - Virus, Adeno 1
 - DNA Replication, 77-6986
- Virus, Adeno 12**
 - DNA, Viral
 - Cell Transformation, Neoplastic, 77-6988
 - DNA-DNA Hybridization, 77-6988
 - Isolation and Characterization, 77-6988
 - Reassociation Kinetics, 77-6988
- Virus, Avian Erythroblastosis**
 - Leukemia
 - Sarcoma, 77-6915
- Virus, Avian Leukosis**
 - IgG
 - Immune Response, 77-6992
 - IgM
 - Immune Response, 77-6992
 - Leukemia
 - Virus Subgroup, 77-6918
 - Reverse Transcriptase
 - DNA Replication, 77-6916
 - Nucleotide Incorporation, 77-6916
 - Temperature Sensitive Mutants, 77-6916
 - Viral Proteins
 - Tissue Specificity, 77-6992
 - Virus Replication
 - Immune Response, 77-6992
- Virus, Avian Leukosis-Sarcoma**
 - DNA, Viral
 - Binding Sites, 77-6923
 - Endonucleases
 - Binding Sites, 77-6923
 - DNA, Viral, 77-6923
 - Glycoproteins
 - Antigenic Determinants, 77-6919
- Virus, Avian Myeloblastosis**
 - Peptides
 - Cells, Cultured, 77-6926
- Virus, Avian Reticuloendotheliosis**
 - DNA, Viral
 - Cytopathogenic Effect, Viral, 77-6923
 - Endonucleases
 - Binding Sites, 77-6923
 - Cytopathogenic Effect, Viral, 77-6923
 - DNA, Viral, 77-6923
- Virus, Avian Sarcoma**
 - Cell Transformation, Neoplastic
 - DNA, Viral, 77-6921
 - DNA, Viral
 - DNA-RNA Hybridization, 77-6919
- Virus, Avian Sarcoma (cont'd)**
 - Glycoproteins
 - Deletion Mutant, 77-6919
 - Reverse Transcriptase
 - DNA Replication, 77-6916
 - Nucleotide Incorporation, 77-6916
 - Temperature Sensitive Mutants, 77-6916
 - RNA, Viral
 - Viral Proteins, 77-6922
 - Viral Proteins
 - Cell-Free Synthesis, 77-6922
- Virus, B77**
 - Antigenic Determinants
 - Cell Transformation, Neoplastic, 77-6972
 - Viral Proteins
 - Cell Transformation, Neoplastic, 77-6972
 - Isolation and Characterization, 77-6920, 77-6972
 - Temperature Sensitive Mutants, 77-6972
 - Virus, Murine Leukemia
 - Antigen-Antibody Reactions, 77-6972
- Virus, Baboon**
 - Reverse Transcriptase
 - Isolation and Characterization, 77-7006
- Virus, RD-114**
 - Antibody Specificity, 77-7006
- Virus, Bovine Leukemia**
 - Lymphocytes
 - Antigens, Viral, 77-6938
 - Concanavalin A, 77-6938
 - Lymphosarcoma
 - Antigens, Viral, 77-6938
 - Concanavalin A, 77-6938
- Virus, C-Type RNA Tumor**
 - Antigens, Viral
 - Cell Transformation, Neoplastic, 77-6966
 - Immune Serums, 77-6966
 - Virus Replication, 77-6966
 - Carcinoma, Epidermoid
 - Cholanthrene, 3-Methyl-, 77-7083
 - Chondrosarcoma
 - RNA, Viral, 77-6990
 - Virus-Like Particles, 77-6990
 - Leukemia
 - Review, 77-6642
 - Liposarcoma
 - Virus Replication, 77-6976
 - Lung Neoplasms
 - Virus Replication, 77-6976
 - Lymphosarcoma
 - Isolation and Characterization, Mouse, 77-6975
 - Reverse Transcriptase, 77-6975
 - Neuroblastoma
 - Virus Replication, 77-6976
 - RNA, Viral
 - Carrier Proteins, 77-6932
 - Viral Proteins
 - Genetics, 77-7007
 - Isolation and Characterization, 77-7007
 - Virus, Moloney Murine Leukemia
 - Antigen-Antibody Reactions, 77-6966
 - Virus, Rauscher Murine Leukemia
 - Reverse Transcriptase, 77-6954
- Virus, D-Type Retra**
 - see Virus, D-Type RNA Tumor

Virus, D-Type RNA Tumor

- Cells, Cultured
 - Isolation and Characterization, Review, 77-6638
- RNA, Viral
 - Isolation and Characterization, Review, 77-6638
- Virus, Il'in-Bykovskii
 - Antigens, Viral, 77-7005

Virus, Epstein-Barr

- Agammaglobulinemia
 - Immunodeficiency, 77-7121
- Antigen-Antibody Reactions
 - Lymphotoxin, 77-7054
- Antigens, Viral
 - Aminopterin, 77-6994
 - Complement Fixation, 77-6993
 - DNA, Binding, 77-6993
 - Hypoxanthine, 77-6994
 - Radioimmunoassay, 77-6995
 - Ultrastructural Study, 77-6996
 - Uridine, 2'-Deoxy-5-iodo-, 77-6994
- Ataxia Telangiectasia
 - Antibodies, Viral, 77-6991
 - Antigen-Antibody Reactions, 77-6991
 - Genetics, 77-6991
 - Immune Response, 77-6991
- Burkitt's Lymphoma
 - Antibodies, Viral, 77-7055
 - Antigen-Antibody Reactions, 77-7055
 - Antigen-Antibody Reactions, Review, 77-6645
 - Antigens, Viral, 77-6998, 77-6999
 - Carcinogenic Potential, Review, 77-6645
 - Cells, Cultured, 77-6999
 - Epidemiology, 77-6998
 - Epidemiology, Review, 77-6644
 - Nucleic Acid Hybridization, 77-6998
 - Seroepidemiology, Review, 77-6643
 - Virus Replication, 77-6999
- Cell Membrane
 - Antigens, Viral, 77-6995
- Hodgkin's Disease
 - Antigen-Antibody Reactions, 77-6994
- Infectious Mononucleosis
 - Epidemiology, 77-7155
 - Immunodeficiency, 77-7121
- Leukemia, Lymphocytic
 - Antigen-Antibody Reactions, 77-6994
- Lymphatic Diseases
 - Immunodeficiency, 77-7121
- Lymphocytes
 - Ultrastructural Study, 77-6996
- Lymphoma
 - Antigen-Antibody Reactions, 77-6994
 - Antigens, Viral, 77-6994
 - Immunodeficiency, 77-7121
 - Immunologic Deficiency Syndromes, 77-6646
 - B-Lymphocytes, 77-6646
- Methanol
 - Antibodies, Viral, 77-7055
- Nasopharyngeal Neoplasms
 - Antigen-Antibody Reactions, 77-6994, 77-7054
 - Antigen-Antibody Reactions, Review, 77-6645
 - Carcinogenic Potential, Review, 77-6645
 - Carcinoma, 77-6996, 77-6997, 77-7054
 - Epidemiology, Review, 77-6644
 - Isolation and Characterization, 77-6996
 - Seroepidemiology, Review, 77-6643
 - Ultrastructural Study, 77-6997

Virus, Epstein-Barr (cont'd)

- Sarcoma, Reticulum Cell
 - Antigen-Antibody Reactions, 77-6994
- Tonsillar Neoplasms
 - Seroepidemiology, Review, 77-6643
- Virus, Measles
 - Immunodeficiency, 77-7121

Virus, Feline Leukemia

- Antigens, Viral
 - Antigen-Antibody Reactions, 77-7082
 - Cell Transformation, Neoplastic, 77-6934
 - Cells, Cultured, 77-6935, 77-6957
 - Solubilization, 77-7082
 - Cell Membrane
 - Antigens, Viral, 77-7082
 - Child
 - Horizontal Transmission, Review, 77-6641
 - Leukemia
 - Review, 77-6642
 - Lymphosarcoma
 - Seroepidemiology, Review, 77-6640
 - Mammary Neoplasms, Experimental
 - Antigens, Viral, 77-6933
 - Virus-Like Particles, 77-6933
 - Pregnancy
 - Horizontal Transmission, Review, 77-6641
 - RNA, Viral
 - Cells, Cultured, 77-6935
 - Saliva
 - Horizontal Transmission, Review, 77-6640
 - Urine
 - Horizontal Transmission, Review, 77-6640
 - Viral Proteins
 - 2-Azetidinecarboxylic Acid, 77-6936
 - Fluoride, Phenylmethylsulfonyl-, 77-6936
 - Isolation and Characterization, 77-6936
 - Pactamycin, 77-6936
 - Peptides, 77-6936
 - Virus, Friend Murine Leukemia
 - Antigen-Antibody Reactions, 77-6960
 - Virus, Moloney Murine Sarcoma
 - Antigenic Determinants, 77-6969
 - Virus Replication
 - Cells, Cultured, 77-6935
- Virus, Feline Sarcoma**
- Antigens, Viral
 - Cell Transformation, Neoplastic, 77-6934
- Virus, Friend Murine Leukemia**
- Antigens, Viral
 - Cells, Cultured, 77-6957, 77-6958
 - Bone Marrow Cells
 - Virus Replication, 77-6937
 - Erythroleukemia
 - Reverse Transcriptase, 77-6956
 - Erythropoiesis
 - Cell Transformation, Neoplastic, 77-6956
 - Glycoproteins
 - Antibody Specificity, 77-6960
 - Antigen-Antibody Reactions, 77-6960
 - Immune Response, 77-6960
 - Hematopoietic Stem Cells
 - Cell Differentiation, 77-6937
 - Leukemia
 - Immunity, Cellular, 77-7050
 - Protein Kinase
 - Translational Inhibitor, Isolation and Characteriza-

- irus, Friend Murine Leukemia (cont'd)**
 - tion, 77-7188
 - Reverse Transcriptase
 - Erythropoiesis, 77-6956
 - Methane, Sulfinylbis-, 77-6956
 - Uridine, 5-Bromo-2'-deoxy-, 77-6956
 - RNA Replication
 - Translational Inhibitor, Isolation and Characterization, 77-7188
 - Virus, Feline Leukemia
 - Antigen-Antibody Reactions, 77-6960
 - Virus, Gross Murine Leukemia
 - Antibody Specificity, 77-7043
- irus, Friend Spleen Focus-Forming**
 - Virus, Murine Leukemia
 - DNA-RNA Hybridization, 77-6959
 - Virus, Recombinant, 77-6959
- irus, Gibbon Ape Lymphoma**
 - Antigens, Viral
 - Cells, Cultured, 77-6957
- irus, Gross Murine Leukemia**
 - Antigens, Viral
 - Cells, Cultured, 77-6957
 - Viral Proteins, 77-6947
 - Immune Serums
 - Antigen-Antibody Reactions, 77-7043
 - Viral Proteins
 - Isolation and Characterization, 77-6947
 - Viral Vaccines
 - Antibody Formation, 77-7043
 - Virus, Friend Murine Leukemia
 - Antibody Specificity, 77-7043
- irus, Harvey Murine Sarcoma**
 - Cyclophosphamide
 - Carcinogenic Activity, 77-6970
 - Dose-Response Study, 77-6970
- irus, Helper**
 - Virus, Adeno 1
 - DNA Replication, 77-6986
- irus, Hepatitis**
 - Hepatoma
 - Antigen-Antibody Reactions, 77-6989
 - Epidemiology, Uganda, 77-6989
- irus, Herpes Lucke**
 - Kidney Neoplasms
 - Adenocarcinoma, 77-7194
 - Isoenzymes, 77-7194
 - Muramidase, 77-7194
- irus, Herpes Saimiri**
 - Acetic Acid, Phosphono-
 - Virus Replication, 77-7004
 - Benzo(a)pyrene
 - Virus Replication, 77-7004
 - Cholanthrene, 3-Methyl-
 - Virus Replication, 77-7004
- irus, Herpes Simplex 1**
 - Antibodies, Viral
 - Immunity, Cellular, 77-7052, 77-7053
 - Cytosine, 1- β -D-Arabinofuranosyl-, Monohydrochloride
 - Virus Replication, 77-7002
 - DNA, Viral
 - Urea, Hydroxy-, 77-7001
 - Immunity, Cellular
- Virus, Herpes Simplex 1 (cont'd)**
 - Effector Cell, Isolation and Characterization
 - 77-7052
 - Immunoglobulins, Fc
 - Immunity, Cellular, 77-7052
 - Lymphocyte Depletion
 - Immunity, Cellular, 77-7052
 - Lymphocytes
 - Immunity, Cellular, 77-7053
 - Ultraviolet Rays
 - DNA Repair, 77-7002
 - Virus Replication, 77-7002
 - Urea, Hydroxy-
 - Virus Replication, 77-7002
 - Uridine, 2'-Deoxy-5-fluoro-
 - Virus Replication, 77-7002
 - Viral Proteins
 - Cell Transformation, Neoplastic, 77-7000
 - Concanavalin A, 77-7000
 - Isolation and Characterization, 77-7000
 - Virus Replication
 - Urea, Hydroxy-, 77-7001
- Virus, Herpes Simplex 2**
 - Carcinoma
 - Immune Response, Hamster, 77-7045
 - Sarcoma
 - Neoplasm Transplantation, 77-7003
- Virus, Il'in-Bykovskii**
 - Virus, D-Type RNA Tumor
 - Antigens, Viral, 77-7005
 - Virus, Mason-Pfizer Monkey
 - Antigen-Antibody Reactions, 77-7005
 - Antigenic Determinants, 77-7005
- Virus, Kirsten Murine Sarcoma**
 - Adenoma
 - Cell Transformation, Neoplastic, 77-6974
 - Antigen-Antibody Reactions
 - Isolation and Characterization, 77-6972
 - Cell Transformation, Neoplastic
 - Glycolipids, 77-7057
 - Heparin, 77-6973
 - Colonic Neoplasms
 - Cell Transformation, Neoplastic, 77-6652
 - Genetics, 77-6974
 - Fibroblasts
 - Cell Transformation, Neoplastic, 77-6974
- Virus-Like Particles**
 - Chondrosarcoma
 - Virus, C-Type RNA Tumor, 77-6990
 - Fibrosarcoma
 - Endoplasmic Reticulum, 77-7012
 - Virus, SV40, 77-7012
 - Lymphoma
 - Virus, Measles, 77-7121
 - Lymphosarcoma
 - Cells, Cultured, 77-7124
 - Mammary Neoplasms, Experimental
 - Virus, Feline Leukemia, 77-6933
 - Virus, RD-114, 77-6933
 - Virus, Moloney Murine Leukemia
 - Genome, 77-6967
 - Virus, SV40
 - Protein Synthesis, 77-7012
- Virus, Marek's Disease**
 - Histocompatibility Antigens

- Virus, Marek's Disease (cont'd)**
 Graft vs Host Reaction, 77-7089
- Virus, Marek's Disease Herpes**
 Histocompatibility Antigens
 Immune Response, 77-7089
 Isoantigens
 Graft vs Host Reaction, 77-7089
 T-Lymphocytes
 Immune Response, 77-7065
 Lymphocyte Depletion, 77-7065
 Lymphoma
 T-Lymphocytes, 77-7065
 Viral Vaccines
 Immune Response, 77-7042
 Viral Interference, 77-7042
- Virus, Mason-Pfizer Monkey**
 Virus, Il'in-Bykovskii
 Antigen-Antibody Reactions, 77-7005
 Antigenic Determinants, 77-7005
- Virus, Measles**
 Agammaglobulinemia
 Immunodeficiency, 77-7121
 Infectious Mononucleosis
 Immunodeficiency, 77-7121
 Lymphatic Diseases
 Immunodeficiency, 77-7121
 Lymphoma
 Immunodeficiency, 77-7121
 Virus-Like Particles, 77-7121
 Virus, Epstein-Barr
 Immunodeficiency, 77-7121
- Virus, Meningitis**
 Hematopoietic Stem Cells
 Colony Formation, 77-6944
 Erythropoietin, 77-6944
 Interferon, 77-6944
 Iron, 77-6944
 Radiation, Ionizing
 Interferon, 77-6944
- Virus, Moloney Murine Leukemia**
 Antigens, Neoplasm
 Antigen-Antibody Reactions, 77-7085
 Lymphocyte Cytotoxicity, 77-7085
 Migration Inhibitory Factor, 77-7085
 Antigens, Viral
 Cells, Cultured, 77-6957
 Bone Marrow Cells
 Virus Replication, 77-6937
 Genome
 Plaque Assay, 77-6967
 Temperature Sensitive Mutants, 77-6967
 Hematopoietic Stem Cells
 Cell Differentiation, 77-6937
 Lymphoma
 Antigens, Neoplasm, 77-7085
 Ploidy
 Temperature Sensitive Mutants, 77-6967
 Virus, C-Type RNA Tumor
 Antigen-Antibody Reactions, 77-6966
 Virus-Like Particles
 Genome, 77-6967
 Virus, Moloney Murine Sarcoma
 Virus, Recombinant, 77-6967
- Virus, Moloney Murine Sarcoma**
 DNA, Viral
 DNA-RNA Hybridization, 77-6968
 Endonucleases, 77-6968
 Isolation and Characterization, 77-6968
 Virus Replication, 77-6968
 Immunity, Cellular
 Lymphocytes, 77-7176
 Lymphocytes
 Cryopreservation, 77-7176
 Methane, Sulfinylbis-
 Lymphocytes, 77-7176
 Viral Proteins
 Cell Transformation, Neoplastic, 77-6969
 Isolation and Characterization, 77-6969
 Virus, Feline Leukemia
 Antigenic Determinants, 77-6969
 Virus, Moloney Murine Leukemia
 Virus, Recombinant, 77-6967
- Virus, Murine Leukemia**
 Antigenic Determinants
 Mouse, AKR/New Zealand, 77-6961
 Bone Marrow
 Virus Replication, 77-6945
 Cell Transformation, Neoplastic
 Mouse, AKR, 77-6963
 Glycoproteins
 Virus, Recombinant, 77-6965
 Histocompatibility Antigens
 Immune Response, 77-7088
 Immune Serums
 Antibody Specificity, 77-7043
 Antigen-Antibody Reactions, 77-7043
 Viral Proteins, 77-6961
 Isolation and Characterization
 Mouse, AKR, 77-6963
 Leukemia, Radiation-Induced
 Antigens, Viral, 77-6962
 Bone Marrow Cells, 77-6962
 Precancerous Conditions, 77-6962
 Thymus Neoplasms, 77-6962
 Virus Replication, 77-6962
 Lymphoma
 Mouse, AKR, 77-6963
 Neoplasms, Experimental
 Antigens, Viral, 77-7090
 Histocompatibility Antigens, 77-7090
 Virus, Rauscher Murine Leukemia, 77-6948
 Virus Replication, 77-6948
 Oligonucleotides
 Isolation and Characterization, 77-6946
 Virus, Recombinant, 77-6946
 Spleen
 Virus Replication, 77-6945
 Thymus Gland
 Mouse, Nude, 77-6945
 Virus Replication, 77-6945
 Thymus Neoplasms
 Isolation and Characterization, 77-6965
 Viral Proteins
 Antigenic Determinants, 77-6964
 Ascitic Fluid, 77-6961
 Isolation and Characterization, 77-6961
 Isolation and Characterization, Mouse, AKR
 77-6964
 Viral Vaccines
 Antibody Formation, 77-7043

Virus, Murine Leukemia (cont'd)

- Virus, B77
 - Antigen-Antibody Reactions, 77-6972
- Virus, Friend Spleen Focus-Forming
 - DNA-RNA Hybridization, 77-6959
- Virus, Recombinant
 - Mouse, AKR, 77-6965
- Virus Replication
 - Antigenic Determinants, 77-6964
 - Mouse, AKR, 77-6963
 - Mouse, Nude, 77-6945
- Virus, Xenotropic Murine Leukemia
 - Mouse, Nude, 77-6945

Virus, Murine Mammary Tumor

- Actin
 - Isolation and Characterization, 77-6943
 - Ultrastructural Study, 77-6943
 - Virus Replication, 77-6943
- Antigens, Viral
 - Immune Response, 77-7081
 - Lymphocytes, 77-7081
- Dexamethasone
 - Cells, Cultured, 77-6942
- Hepatoma
 - Antigens, Viral, 77-6942
 - Cells, Cultured, 77-6942
 - DNA, Viral, 77-6941
 - RNA, Viral, 77-6942
 - Virus Replication, 77-6941, 77-6942
- Lymphocyte Depletion
 - Immune Response, 77-7066
- T-Lymphocytes
 - Immune Response, 77-7066
 - Lymphocyte Depletion, 77-7066
- Mammary Neoplasms, Experimental
 - Actin, 77-6943
 - Histological Study, 77-6867
 - Virus, Vesicular Stomatitis, 77-6940
- Thymus Gland
 - Cell Transformation, Neoplastic, 77-7066
- Virus, Vesicular Stomatitis
 - Antigens, Viral, 77-6940

Virus, Papova

- Baboon
 - Isolation and Characterization, 77-7008
- Cell Transformation, Neoplastic
 - Isolation and Characterization, 77-7008

Virus, Polyoma

- Antigens, Neoplasm
 - Cell Membrane, 77-6979
 - Temperature Sensitive Mutants, 77-6979
- Antigens, Viral
 - Embryo, Hamster, 77-7091
 - Isolation and Characterization, 77-7091
- Brain Neoplasms
 - Medulloblastoma, 77-6983
 - Pinealoma, 77-6983
- Cell Transformation, Neoplastic
 - Aminotransferases, 77-7015
 - Fibroblasts, 77-6981
 - Temperature Sensitive Mutants, 77-6977
- DNA, Viral
 - DNA-RNA Hybridization, 77-6977
 - Temperature Sensitive Mutants, 77-6977
- Fibroblasts

Virus, Polyoma (cont'd)

- DNA-RNA Hybridization, 77-6978
- Nucleic Acids, 77-6978
- RNA Replication, 77-6978
- Fibrosarcoma
 - Antigens, Viral, 77-7091
 - Histocompatibility Antigens, 77-7091
- Histocompatibility Antigens
 - Embryo, Hamster, 77-7091
 - Isolation and Characterization, 77-7091
- Neoplasms, Experimental
 - Galactosyltransferases, 77-6980
- Neoplasms, Multiple Primary
 - Animal Model, Mouse, Review, 77-6639
- RNA Replication
 - Actinomycin D, 77-6978
 - α -Amanitine, 77-6978
 - Temperature Sensitive Mutants, 77-6977
- Stress
 - Immune Response, 77-6908
 - Ultrasonics, 77-6908
- Ultrasonics
 - Transplantation Immunology, 77-6908
- Viral Proteins
 - Cell Membrane, 77-6979
 - Cell Transformation, Neoplastic, 77-6979
 - Temperature Sensitive Mutants, 77-6979
- Viral Vaccines
 - Transplantation Immunology, 77-6908
 - Ultrasonics, 77-6908

Virus, Polyoma, BK

- DNA, Viral
 - Cell Transformation, Neoplastic, 77-6982
 - Isolation and Characterization, 77-6982

Virus, Polyoma, JC

- Brain Neoplasms
 - Carcinogenic Effect, Hamster, 77-6983
- Leukoencephalopathy, Progressive Multifocal
 - Antigens, Viral, 77-6984

Virus, Radiation Leukemia

- Histocompatibility Antigens
 - Immune Response, 77-7088

Virus, Rauscher Murine Leukemia

- Antibodies
 - Isolation and Characterization, 77-7056
- Antigens, Viral
 - Cells, Cultured, 77-6957
- Hematopoietic Stem Cells
 - Cell Differentiation, 77-6950
- Hodgkin's Disease
 - DNA-RNA Hybridization, 77-6952
 - Reverse Transcriptase, 77-6953
- Interferon
 - Immune Response, 77-6949
 - Virus Replication, 77-6949
- Leukemia
 - DNA-RNA Hybridization, 77-6952
- Methanesulfonic Acid, Isopropyl Ester
 - Hematopoietic Stem Cells, 77-6950
 - Splenomegaly, 77-6950
- Multiple Myeloma
 - DNA-RNA Hybridization, 77-6952
- Neoplasms, Experimental
 - Virus, Murine Leukemia, 77-6948
- Quinoline, 4-Nitro-, 1-Oxide

Virus, Rauscher Murine Leukemia (cont'd)

- Cell Transformation, Neoplastic, 77-6858
- DNA Repair, 77-6858

Reverse Transcriptase

- DNA, 77-6954
- DNA Replication, 77-6951
- Isolation and Characterization, 77-6951
- Ribonuclease, 77-6951

Streptovaricins

- Reverse Transcriptase, 77-6955
- Splenomegaly, 77-6955
- Virus Replication, 77-6955

Thymoma

- Transplantation Immunology, 77-7068

Ultraviolet Rays

- DNA Repair, 77-6858

Virus, C-Type RNA Tumor

- Reverse Transcriptase, 77-6954

Virus, RD-114**Mammary Neoplasms, Experimental**

- Antigens, Viral, 77-6933
- Virus-Like Particles, 77-6933

Virus, Baboon

- Antibody Specificity, 77-7006

Virus, Recombinant

- Virus, Moloney Murine Leukemia
- Virus, Moloney Murine Sarcoma, 77-6967

Virus Replication

- Acetic Acid, Phosphono-
 - Virus, Herpes Saimiri, 77-7004
- Benzo(a)pyrene
 - Virus, Herpes Saimiri, 77-7004
- Burkitt's Lymphoma
 - Virus, Epstein-Barr, 77-6999
- Cholanthrene, 3-Methyl-
 - Virus, Herpes Saimiri, 77-7004
- Leukemia, Radiation-Induced
 - Radiation, Ionizing, 77-6962
 - Virus, Murine Leukemia, 77-6962
- Liposarcoma
 - Transplantation, Heterologous, 77-6976
 - Ultrastructural Study, C-Type Particles, 77-6976
 - Virus, C-Type RNA Tumor, 77-6976
- Lung Neoplasms
 - Transplantation, Heterologous, 77-6976
 - Ultrastructural Study, C-Type Particles, 77-6976
 - Virus, C-Type RNA Tumor, 77-6976
- Neoplasms, Experimental
 - Virus, Murine Leukemia, 77-6948
- Neuroblastoma
 - Transplantation, Heterologous, 77-6976
 - Ultrastructural Study, C-Type Particles, 77-6976
 - Virus, C-Type RNA Tumor, 77-6976
- Virus, Avian Leukosis
 - Immune Response, 77-6992
- Virus, C-Type RNA Tumor
 - Antigens, Viral, 77-6966
- Virus, Feline Leukemia
 - Cells, Cultured, 77-6935
- Virus, Friend Murine Leukemia
 - Bone Marrow Cells, 77-6937
- Virus, Herpes Simplex 1
 - Cytosine, 1- β -D-Arabinofuranosyl-, Monohydrochloride, 77-7002
 - Ultraviolet Rays, 77-7002
 - Urea, Hydroxy-, 77-7001, 77-7002

Virus Replication (cont'd)

- Uridine, 2'-Deoxy-5-fluoro-, 77-7002

Virus, Moloney Murine Leukemia

- Bone Marrow Cells, 77-6937

Virus, Moloney Murine Sarcoma

- DNA, Viral, 77-6968

Virus, Murine Leukemia

- Antigenic Determinants, 77-6964
- Bone Marrow, 77-6945
- Mouse, AKR, 77-6963
- Mouse, Nude, 77-6945
- Spleen, 77-6945
- Thymus Gland, 77-6945

Virus, Murine Mammary Tumor

- Actin, 77-6943
- Hepatoma, 77-6941, 77-6942

Virus, Rauscher Murine Leukemia

- Glutarimide, 3-(2-Hydroxy-2-(5-hydroxy-3,5-dimethyl-2-oxocyclohex, 77-6955
- Interferon, 77-6949
- Streptovaricin C, 77-6955
- Streptovaricins, 77-6955

Virus, Shope Rabbit Fibroma

- Cell Aggregation, 77-6939
- Cells, Cultured, 77-6939
- Ultraviolet Rays, 77-6939

Virus, SV40

- African Green Monkey Cells, 77-7013
- Hybrid Cells, 77-7013
- Temperature Sensitive Mutants, 77-7026
- Viral Proteins, 77-7027

Virus, Vesicular Stomatitis

- Ultraviolet Rays, 77-6939

Virus, Rous Sarcoma**Cartilage**

- Acetic Acid, 77-6929
- Cell Transformation, Neoplastic, 77-6929
- Glucose, 2-Deoxy-, 77-6929
- Hyaluronic Acid, 77-6929

Cell Adhesion

- Cell Transformation, Neoplastic, 77-6925

Cell Membrane

- Binding Sites, 77-6917
- Proteins, 77-6925
- Trypsin, 77-6917

Cell Transformation, Neoplastic

- Aminotransferases, 77-7015
- Biological Transport, 77-6931
- Chick Embryo, 77-6930
- Temperature Sensitive Mutants, 77-6925, 77-6929

Chick Embryo

- DNA-DNA Hybridization, 77-6930

Chondroitin

- Cell Transformation, Neoplastic, 77-6928

Fibroblasts

- Cell Adhesion, 77-6925

Glucose

- Binding Factor, 77-6927
- Cell Transformation, Neoplastic, 77-6927
- Hyaluronic Acid

- Temperature Sensitive Mutants, 77-6928

Karyotyping

- Cell Transformation, Neoplastic, 77-6930
- Chick Embryo, 77-6930

Mucopolysaccharides

- Cartilage, 77-6928
- Cell Transformation, Neoplastic, 77-6928

- Virus, Rous Sarcoma (cont'd)**
 - Temperature Sensitive Mutants, 77-6928
 - Osteopetrosis
 - Virus Subgroup, 77-6918
 - Peptides
 - Cells, Cultured, 77-6926
 - Phosphoproteins
 - RNA, Viral, 77-6932
 - Proteins
 - Cell Transformation, Neoplastic, 77-6925
 - RNA, Viral
 - Carrier Proteins, 77-6932
 - DNA Nucleotidyltransferases, 77-6924
 - DNA Replication, 77-6924
 - DNA-RNA Hybridization, 77-6924
 - Sarcoma
 - DNA Replication, 77-7189
 - Temperature Sensitive Mutants, 77-6918
 - Virus Subgroup, 77-6918
 - Ultraviolet Rays
 - Phosphoproteins, 77-6932
 - Viral Proteins
 - Isolation and Characterization, 77-6926
- Virus, Shope Rabbit Fibroma**
 - Cell Aggregation
 - Virus Replication, 77-6939
 - Cells, Cultured
 - Virus Replication, 77-6939
 - Ultraviolet Rays
 - Cell Aggregation, 77-6939
 - Virus Replication, 77-6939
- Virus, Simian 5**
 - Viral Proteins
 - Isolation and Characterization, 77-7009
- Virus, SV40**
 - Antigens, Neoplasm
 - Cell Transformation, Neoplastic, 77-7070
 - Antigens, Viral
 - DNA, Binding, 77-7026
 - Temperature Sensitive Mutants, 77-7026
 - Ataxia Telangiectasia
 - Chromosomes, 77-7139
 - Cell Transformation, Neoplastic
 - Ataxia Telangiectasia, 77-7019
 - Fibroblasts, 77-7139
 - Heparin, 77-6973
 - Phenotype, 77-7010
 - Temperature Sensitive Mutants, 77-7026
 - Chromatin
 - Cell-Free Assembly, 77-7028
 - Chromosomes
 - Chromatin, 77-7029
 - DNA, Viral, 77-7029, 77-7139
 - Isolation and Characterization, 77-7029
 - Chromosomes, Human, 16-18
 - Cell Transformation, Neoplastic, 77-7011
 - DNA, Binding
 - Temperature Sensitive Mutants, 77-7026
 - DNA Replication
 - Cell Cycle Kinetics, 77-7022
 - Cell Transformation, Neoplastic, 77-7022
 - Cycloheximide, 77-7022
 - DNA, Viral
 - Base Sequence, 77-7017
 - Chromatin, 77-7028
 - DNA Replication, 77-7018
- Virus, SV40 (cont'd)**
 - DNA-RNA Hybridization, 77-7018
 - Hairpin Turns, 77-7025
 - Isolation and Characterization, 77-7014
 - Nucleic Acid Denaturation, 77-7025
 - Psoralen, 4,5',8-Trimethyl-, 77-7025
 - Temperature Sensitive Mutants, 77-7020, 77-7021
 - Ultrastructural Study, 77-7025
 - Virus, Recombinant, 77-7020, 77-7021
 - Endonucleases
 - Virus, Recombinant, 77-7021
 - Fibrosarcoma
 - Ultrastructural Study, 77-7012
 - Virus-Like Particles, 77-7012
 - Histocompatibility Antigens
 - Antigens, Neoplasm, 77-7084
 - Cell Transformation, Neoplastic, 77-7070
 - Temperature Sensitive Mutants, 77-7084
 - Histones
 - Isolation and Characterization, 77-7014
 - Hybrid Cells
 - Antigens, Viral, 77-7011
 - Cell Aggregation, 77-7010
 - Cell Transformation, Neoplastic, 77-7010, 77-7011, 77-7013, 77-7141
 - Chromosomes, Human, 6-12, 77-7010
 - Chromosomes, Human, 16-18, 77-7011
 - DNA Replication, 77-7010
 - Temperature Sensitive Mutants, 77-7010
 - Ultrastructural Study, 77-7141
 - Virus Replication, 77-7013
 - Lymphocytes
 - Cytotoxicity, 77-7070
 - Macrophages
 - Hybrid Cells, 77-7141
 - Neurofibroma
 - Chromosomes, 77-7139
 - Nucleotides
 - Base Sequence, 77-7016
 - Precancerous Conditions
 - Chromosomes, 77-7139
 - Proteins
 - Isolation and Characterization, 77-7023, 77-7024
 - Sarcoma
 - Histocompatibility Antigens, 77-7045
 - Viral Proteins
 - Cell Transformation, Neoplastic, 77-7027
 - Phosphorylation, 77-7027
 - Protein A, Isolation and Characterization, 77-7027
 - Temperature Sensitive Mutants, 77-7027
 - Virus Replication, 77-7027
 - Virus-Like Particles
 - Protein Synthesis, 77-7012
 - Virus Replication
 - African Green Monkey Cells, 77-7013
 - Temperature Sensitive Mutants, 77-7026
- Virus, Vesicular Stomatitis**
 - Mammary Neoplasms, Experimental
 - Virus, Murine Mammary Tumor, 77-6940
 - Ultraviolet Rays
 - Virus Replication, 77-6939
 - Virus, Murine Mammary Tumor
 - Antigens, Viral, 77-6940
- Virus, Xenotropic Murine Leukemia**
 - Leukemia
 - Mouse, Nude, 77-6945

Virus, Xenotropic Murine Leukemia (cont'd)

Virus, Murine Leukemia
Mouse, Nude, 77-6945

Vitamin C

see Ascorbic Acid

Vitamin E

Antipyrene, 4-(Dimethylamino)-
Nitrous Acid, Sodium Salt, 77-6717
Dimethylamine, *N*-Nitroso-
Gastric Juice, 77-6717
Nitrous Acid, Sodium Salt
Alanine Aminotransferase, 77-6717
Antipyrene, 4-(Dimethylamino)-, 77-6717
Gastric Juice, 77-6717

Water, Heavy

Bone Marrow Cells
Chromosome Aberrations, 77-7138
Erythropoiesis, 77-7138
Chromosome Aberrations
Precancerous Conditions, 77-7138
Leukemia
Precancerous Conditions, 77-7138

Water Pollutants

Acetic Acid, Nitritotri-
Ozone, 77-6798
Ethyl Alcohol
Ozone, 77-6798
Hydrazine, 1,1-Diphenyl-
Ozone, 77-6798
Hydroquinone
Ozone, 77-6798
Phenol
Ozone, 77-6798
Toluene, 2,4-Dinitro-
Ozone, 77-6798

Xeroderma Pigmentosum

Caffeine
DNA Repair, 77-6903
DNA Repair
Cells, Cultured, 77-6792
Complementation Group, 77-6903
Ultraviolet Rays
Caffeine, 77-6903
DNA Repair, 77-6903

Chemical Abstracts Service Registry Number Index

- 50-00-0, 77-6774
- 50-02-2, 77-6755, 77-6942, 77-7199
- 50-06-6, 77-6678, 77-6732, 77-6753
77-6770, 77-6789, 77-6833
77-6837, 77-7200
- 50-07-7, 77-7070
- 50-18-0, 77-6970, 77-7069, 77-7126
- 50-27-1, 77-7200
- 50-28-2, 77-6618, 77-6692, 77-6695
77-6696, 77-6834, 77-6865
77-6867, 77-6868, 77-6875
77-7116, 77-7200
- 50-29-3, 77-6821
- 50-32-8, 77-6626, 77-6683, 77-6701
77-6719, 77-6720, 77-6721
77-6722, 77-6723, 77-6724
77-6726, 77-6727, 77-6728
77-6729, 77-6730, 77-6731
77-6732, 77-6733, 77-6734
77-6735, 77-6736, 77-6737
77-6738, 77-6739, 77-6740
77-6741, 77-6793, 77-6795
77-6796, 77-6802, 77-6813
77-6830, 77-7004, 77-7048
77-7068, 77-7144
- 50-67-9, 77-6687
- 50-76-0, 77-6608, 77-6822, 77-6978
- 50-81-7, 77-6679, 77-6717
- 50-89-5, 77-6702
- 50-91-9, 77-6608, 77-7002
- 50-99-7, 77-6927, 77-7196
- 51-03-6, 77-6796
- 51-21-8, 77-6608, 77-6863
- 51-31-0, 77-6747
- 51-35-4, 77-7146
- 51-41-2, 77-6653, 77-6687
- 51-43-4, 77-6653, 77-6747
- 51-61-6, 77-6687
- 51-75-2, 77-6795, 77-6863
- 51-79-6, 77-6878, 77-6879
- 51-84-3, 77-6653
- 52-90-4, 77-6779
- 53-16-7, 77-6876
- 53-70-3, 77-6626, 77-6793
- 53-86-1, 77-6755
- 53-95-2, 77-6658, 77-6832, 77-6833
77-6834, 77-6893
- 53-96-3, 77-6601, 77-6658, 77-6799
77-6801, 77-6802, 77-6833
77-6834, 77-6835, 77-6837
77-6893, 77-7109
- 54-11-5, 77-6701, 77-6705, 77-6707
77-6758
- 54-16-0, 77-6687
- 54-42-2, 77-6694
- 54-62-6, 77-6994
- 55-18-5, 77-6612, 77-6629, 77-6658
77-6765, 77-6766, 77-6767
77-6768, 77-6769, 77-6770
77-6776, 77-6794, 77-6801
- 55-80-1, 77-6658, 77-6845, 77-6846
77-6848, 77-7061, 77-7109
- 56-23-5, 77-6823
- 56-49-5, 77-6678, 77-6679, 77-6680
77-6687, 77-6705, 77-6732
77-6741, 77-6751, 77-6752
77-6753, 77-6754, 77-6755
77-6770, 77-6793, 77-6800
77-6833, 77-7004, 77-7047
77-7059, 77-7083, 77-7086
77-7087, 77-7130
- 56-53-1, 77-6602, 77-6615, 77-6867
77-6868, 77-6869, 77-6870
77-6871, 77-6872, 77-7157
- 56-55-3, 77-6687, 77-6699, 77-6721
77-6756
- 56-57-5, 77-6749, 77-6792, 77-6795
77-6802, 77-6858, 77-6860
77-6861, 77-7144
- 56-65-5, 77-6750, 77-7192
- 56-75-7, 77-6829
- 57-11-4, 77-6701
- 57-13-6, 77-6812
- 57-57-8, 77-6793
- 57-63-6, 77-7110, 77-7159
- 57-83-0, 77-6617, 77-6692, 77-6695
77-6868, 77-6875, 77-7159
- 57-85-2, 77-6876
- 57-97-6, 77-6619, 77-6683, 77-6686
77-6687, 77-6688, 77-6689
77-6690, 77-6691, 77-6692
77-6693, 77-6694, 77-6695
77-6696, 77-6698, 77-6702
77-6733, 77-6743, 77-6794
77-6795, 77-6799, 77-6819
77-6821, 77-7144
- 58-08-2, 77-6903
- 58-15-1, 77-6717, 77-6813
- 58-22-0, 77-6868, 77-7118, 77-7162
- 58-54-8, 77-6732
- 58-55-9, 77-6865, 77-7147
- 58-96-8, 77-7196
- 59-02-9, 77-6717
- 59-05-2, 77-6608
- 59-14-3, 77-6956
- 59-51-8, 77-6765
- 59-89-2, 77-6612, 77-6629, 77-6708
77-6709, 77-6770
- 59-92-7, 77-6619
- 60-11-7, 77-6802, 77-6847
- 60-32-2, 77-7183
- 60-34-4, 77-6854
- 60-92-4, 77-6747, 77-7193
- 61-82-5, 77-6775
- 61-90-5, 77-6702
- 62-50-0, 77-6793, 77-6795
- 62-53-3, 77-6852
- 62-55-5, 77-6788
- 62-75-9, 77-6611, 77-6612, 77-6629
77-6658, 77-6715, 77-6717
77-6769, 77-6770, 77-6771
77-6772, 77-6773, 77-6774
77-6775, 77-6776, 77-6788
77-6794, 77-6800
- 63-05-8, 77-6877
- 63-68-3, 77-6765
- 64-17-5, 77-6610, 77-6775, 77-6798
77-6862, 77-7148
- 64-19-7, 77-6929
- 65-86-1, 77-6678
- 66-27-3, 77-6793, 77-6795
- 66-75-1, 77-6608
- 66-81-9, 77-7022, 77-7184
- 67-21-0, 77-6789
- 67-56-1, 77-6775, 77-7055
- 67-63-0, 77-6777
- 67-68-5, 77-6956, 77-7176, 77-7179
- 68-23-5, 77-6866
- 68-94-0, 77-6994
- 69-74-9, 77-6608, 77-7002, 77-7190
- 70-18-8, 77-6779

- 70-25-7, 77-6710, 77-6711, 77-6712
77-6713, 77-6749, 77-6779
77-6793, 77-6795, 77-7044
77-7144
- 71-23-8, 77-6777
- 71-30-7, 77-7189
- 71-43-2, 77-6819
- 72-14-0, 77-6805
- 72-33-3, 77-6866, 77-7159
- 72-54-8, 77-6822
- 72-55-9, 77-6821
- 73-24-5, 77-6789
- 75-01-4, 77-6601, 77-6607, 77-6622
77-6623, 77-6624, 77-6625
77-6760, 77-6796, 77-6824
77-6825, 77-6826, 77-6827
- 75-09-2, 77-6786
- 75-35-4, 77-6601
- 77-78-1, 77-6792
- 79-81-2, 77-6688
- 81-07-2, 77-6681
- 83-05-6, 77-6821
- 83-79-4, 77-6677
- 83-88-5, 77-6666
- 84-17-3, 77-6780
- 86-01-1, 77-7189
- 86-30-6, 77-6760
- 88-05-1, 77-6849
- 88-19-7, 77-6682
- 90-41-5, 77-6795, 77-6840
- 90-45-9, 77-6851
- 90-98-2, 77-6821
- 91-59-8, 77-6839
- 91-64-5, 77-6813
- 92-67-1, 77-6839
- 92-87-5, 77-6796, 77-6852, 77-6853
- 96-09-3, 77-6753
- 97-00-7, 77-6732
- 97-56-3, 77-6795, 77-6843, 77-6844
- 97-77-8, 77-6767, 77-6775
- 98-50-0, 77-6811
- 98-92-0, 77-6768
- 100-14-1, 77-6732
- 100-75-4, 77-6611, 77-6612, 77-6706
77-6759, 77-6761
- 103-71-9, 77-6683
- 103-84-4, 77-6813
- 107-07-3, 77-6824
- 107-92-6, 77-7179
- 108-05-4, 77-6910
- 108-95-2, 77-6701, 77-6798
- 110-13-4, 77-6846
- 110-16-7, 77-6779
- 110-89-4, 77-6611
- 111-30-8, 77-7040
- 119-93-7, 77-6852
- 121-14-2, 77-6798
- 121-69-7, 77-6852
- 123-31-9, 77-6798
- 123-54-6, 77-6846
- 123-75-1, 77-6611
- 124-40-3, 77-6611
- 126-99-8, 77-6601, 77-6819
- 127-07-1, 77-6608, 77-6787, 77-7001
77-7002
- 127-19-5, 77-7179
- 128-37-0, 77-6837
- 128-44-9, 77-6682
- 128-53-0, 77-6779, 77-7185, 77-7189
- 129-00-0, 77-6802
- 129-20-4, 77-6755
- 139-13-9, 77-6798
- 143-16-8, 77-6763
- 143-50-0, 77-6820
- 153-78-6, 77-6795, 77-6831, 77-6839
- 154-17-6, 77-6929, 77-7181
- 154-93-8, 77-6779
- 189-64-0, 77-6626
- 192-97-2, 77-7048
- 198-55-0, 77-6738
- 205-82-3, 77-6626
- 205-99-2, 77-6626
- 215-58-7, 77-6689, 77-6755
- 224-42-0, 77-6626
- 225-51-4, 77-6684
- 288-13-1, 77-6775, 77-6862
- 289-66-7, 77-7058
- 301-04-2, 77-6805, 77-6811
- 302-01-2, 77-6629
- 303-47-9, 77-6672
- 303-81-1, 77-7190
- 319-84-6, 77-6818
- 329-98-6, 77-6936
- 362-74-3, 77-6750, 77-6865, 77-7147
- 407-25-0, 77-6833
- 431-03-8, 77-6846
- 446-86-6, 77-7035
- 471-29-4, 77-6714
- 486-84-0, 77-6802
- 494-52-0, 77-6707
- 494-97-3, 77-6707
- 521-18-6, 77-7118
- 530-50-7, 77-6798
- 531-82-8, 77-6842, 77-7033
- 540-73-8, 77-6797, 77-6855, 77-6856
77-6857, 77-7174
- 542-88-1, 77-6601
- 548-93-6, 77-6843
- 551-93-9, 77-6838
- 585-08-0, 77-6751
- 586-17-4, 77-6653, 77-6687
- 588-59-0, 77-6802
- 590-96-5, 77-6658, 77-6863
- 592-31-4, 77-6778
- 592-62-1, 77-6797, 77-6862
- 601-77-4, 77-6777
- 604-59-1, 77-6731, 77-6755, 77-6830
- 613-13-8, 77-6795
- 614-00-6, 77-6770
- 615-53-2, 77-6795
- 617-04-9, 77-7191
- 621-64-7, 77-6770, 77-6776
- 629-11-8, 77-6764
- 630-08-0, 77-6705
- 684-93-5, 77-6779, 77-6780, 77-6781
77-6782, 77-6783, 77-6784
77-6792, 77-6795, 77-6797
77-7142
- 759-73-9, 77-6629, 77-6785, 77-6792
77-6897, 77-7137
- 816-57-9, 77-6777
- 817-99-2, 77-6850
- 823-74-5, 77-6842
- 838-95-9, 77-6802
- 869-01-2, 77-6778
- 924-16-3, 77-6770, 77-6776
- 924-46-9, 77-6770
- 926-06-7, 77-6950

930-55-2, 77-6611, 77-6761, 77-6770
 932-83-2, 77-6759, 77-6764
 958-09-8, 77-6725
 961-07-9, 77-6724, 77-6725
 1022-22-6, 77-6821
 1120-71-4, 77-6795
 1133-64-8, 77-6706
 1145-73-9, 77-6802
 1155-38-0, 77-6697
 1162-65-8, 77-6614, 77-6658, 77-6667
 77-6668, 77-6669, 77-6670
 77-6672, 77-6793, 77-6801
 1204-06-4, 77-6838
 1239-45-8, 77-6828
 1308-38-9, 77-6803
 1314-20-1, 77-6622
 1332-21-4, 77-6627, 77-6628, 77-6912
 77-6913, 77-6914, 77-7173
 1404-74-6, 77-6955
 1405-46-5, 77-6936
 1407-15-4, 77-6608
 1606-67-3, 77-6775
 1746-01-6, 77-6754, 77-6813, 77-6814
 2013-22-1, 77-7185
 2050-68-2, 77-6816
 2051-62-9, 77-6816
 2082-84-0, 77-6763
 2257-09-2, 77-6683
 2438-80-4, 77-6971
 2439-10-3, 77-6786
 2517-04-6, 77-6936
 2541-69-7, 77-6697
 2642-82-2, 77-6821
 3012-37-1, 77-6683
 3067-12-7, 77-6726
 3067-13-8, 77-6726
 3067-14-9, 77-6726
 3483-12-3, 77-6779, 77-6846
 3688-53-7, 77-6802, 77-6842
 3697-24-3, 77-6626
 4106-66-5, 77-6839
 4245-77-6, 77-6710, 77-6711
 4408-78-0, 77-7004
 4838-37-3, 77-6877
 5255-75-4, 77-6732

6098-44-8, 77-6793, 77-6834
 6165-21-5, 77-7118
 6292-55-3, 77-6834
 6807-96-1, 77-5510
 7439-89-6, 77-6944
 7439-92-1, 77-6613, 77-6804
 7439-95-4, 77-7196
 7440-08-6, 77-6736
 7440-24-6, 77-6884
 7440-38-2, 77-6622, 77-6623, 77-7171
 7440-44-0, 77-7170
 7440-70-2, 77-7196, 77-7197
 7553-56-2, 77-6632, 77-6883, 77-6884
 7616-22-0, 77-6717
 7631-89-2, 77-6809
 7631-99-4, 77-6778
 7632-00-0, 77-6714, 77-6717, 77-6786
 7647-01-0, 77-6833
 7665-99-8, 77-6779, 77-7193
 7683-59-2, 77-6747
 7697-37-2, 77-6611, 77-6715, 77-6716
 7723-14-0, 77-7135
 7738-94-5, 77-6803
 7758-99-8, 77-6806
 7763-77-1, 77-6824
 7778-50-9, 77-6803
 7782-44-7, 77-6852
 7782-49-2, 77-6809
 7782-77-6, 77-6611, 77-6707, 77-6715
 77-6716, 77-6763
 7784-46-5, 77-6808, 77-6810
 8002-43-5, 77-6763
 8007-45-2, 77-6602
 8063-94-3, 77-6910, 77-7035
 9001-03-0, 77-7187
 9001-05-2, 77-6845
 9001-32-5, 77-7184
 9001-45-0, 77-6912
 9001-60-9, 77-6700
 9001-63-2, 77-7194
 9001-77-8, 77-7132, 77-7134
 9001-78-9, 77-6812, 77-6823
 9001-91-6, 77-7147
 9002-07-7, 77-6917

9002-62-4, 77-6619, 77-6691, 77-6692
 77-6693, 77-6694, 77-6695
 77-6696, 77-6865, 77-7120
 77-7162
 9002-71-5, 77-6634, 77-6635
 9002-72-6, 77-6695
 9002-86-2, 77-6910, 77-7035
 9002-93-1, 77-6763
 9003-98-9, 77-7189
 9004-10-8, 77-6695, 77-6865
 9004-61-9, 77-6928
 9004-67-5, 77-7037
 9005-49-6, 77-6973
 9007-27-6, 77-6928
 9008-11-1, 77-6944, 77-6949
 9035-50-1, 77-6614, 77-6774, 77-6813
 77-6820, 77-6822
 10028-15-6, 77-6798
 10098-97-2, 77-6884
 10102-18-8, 77-6810
 10108-64-2, 77-6811
 10124-36-4, 77-6812
 10588-01-9, 77-6803
 10605-21-7, 77-6786
 11028-71-0, 77-6938, 77-7000, 77-7040
 77-7071, 77-7191
 11056-06-7, 77-6608
 11097-69-1, 77-6830
 12001-28-4, 77-6627, 77-6628, 77-6912
 77-6913, 77-6914, 77-7173
 12001-29-5, 77-6627, 77-6628, 77-6912
 77-6913, 77-6914, 77-7173
 12035-72-2, 77-6807
 12059-95-9, 77-6878, 77-6880
 12172-73-5, 77-6627, 77-6628, 77-6912
 77-6913, 77-6914, 77-7173
 13256-06-9, 77-6770
 13345-21-6, 77-6729, 77-6730, 77-6731
 13345-23-8, 77-6730
 13345-25-0, 77-6742
 13670-17-2, 77-7138
 13967-73-2, 77-6884
 14158-27-1, 77-6884
 14222-46-9, 77-6828
 14301-11-2, 77-6802
 15117-48-3, 77-6879, 77-6881

16561-29-8, 77-6742, 77-6743, 77-6744
77-6745, 77-6746, 77-6747
77-6748, 77-6749, 77-6750

16812-54-7, 77-6807

17068-78-9, 77-6627, 77-6628, 77-6912
77-6913, 77-6914, 77-7173

17573-29-4, 77-6722, 77-6729

18883-66-4, 77-6673, 77-6779, 77-6781
77-6795

20535-83-5, 77-6771

20816-12-0, 77-6906

20830-81-3, 77-6608

22225-32-7, 77-6834

22467-31-8, 77-6672

23109-05-9, 77-6822, 77-6978

23214-92-8, 77-6608

23668-11-3, 77-6936

24554-26-5, 77-6657, 77-6840, 77-6841
77-7033

24928-17-4, 77-6748

25013-16-5, 77-6728, 77-6730

25843-45-2, 77-6864

26241-63-4, 77-6746, 77-6748

29050-11-1, 77-6755

30310-80-6, 77-6761

30641-53-3, 77-6808, 77-6810

31005-02-4, 77-6813

32378-55-5, 77-6828

33953-73-0, 77-6731

35065-27-1, 77-6816

36504-66-2, 77-6742

37114-16-2, 77-6761

37574-47-3, 77-6730

37680-73-2, 77-6816

37691-11-5, 77-6674

53714-56-0, 77-6691

54350-48-0, 77-6685

56892-30-9, 77-6722

57303-99-8, 77-6742

Wiswesser Line Notation Index

- ..H..G, 77-6833 77-6601
- ..H2.CR-O4, 77-6803
- .AS, 77-6622, 77-6623, 77-7171
- .CA, 77-7196, 77-7197
- .CD..G2, 77-6811
- .CD..S-O4, 77-6812
- .FE, 77-6944
- .IL, 77-6632, 77-6883, 77-6884
- .KA2.CR2-O5-Q2, 77-6803
- .MG, 77-7196
- .NA..AS-O-Q3, 77-6809
- .NA..AS-O3, 77-6808, 77-6810
- .NA..N-O2, 77-6714, 77-6717, 77-6786
- .NA..N-O3, 77-6778
- .NA2.SE-O-Q2, 77-6810
- .NI3.S2, 77-6807
- .P, 77-7135
- .PB, 77-6613, 77-6804
- .PO, 77-6736
- .PU, 77-6879, 77-6881
- .PU..O2, 77-6878, 77-6880
- .SE, 77-6809
- .SR, 77-6884
- .TH..O2, 77-6622
- C O, 77-6705
- FXFFV 2O, 77-6833
- GR CG DG EG FR BG DG EG, 77-6816
- GR DVR DG, 77-6821
- GXGGG, 77-6823
- GXGGG YR DG&R DG, 77-6821
- GYGUYR DG&R DG, 77-6821
- GYGU1, 77-6601
- GYGYR DG&R DG, 77-6822
- G1G, 77-6786
- G1O1G, 77-6601
- G1U1, 77-6601, 77-6607, 77-6622, 77-6623, 77-6624, 77-6625
77-6760, 77-6796, 77-6824, 77-6825, 77-6826
77-6827
- G2N1&2G, 77-6795, 77-6863
- L B656 HHJ DMV1, 77-6834
- L B656 HHJ DNQV1, 77-6834
- L B656 HHJ EMV1, 77-6601, 77-6658, 77-6799, 77-6801
77-6802, 77-6833, 77-6834, 77-6835, 77-6837
77-6893, 77-7109
- L B656 HHJ ENQV1, 77-6658, 77-6832, 77-6833, 77-6834
77-6893
- L B666J HHJ EZ, 77-6795, 77-6831, 77-6839
- L C65 K666 1A TJ, 77-6626
- L C666J EZ, 77-6795
- L D6 B66 O666 2AB A&J, 77-6626
- L D6 B666J, 77-6687, 77-6699, 77-6721, 77-6756
- L D6 B666J C J, 77-6619, 77-6683, 77-6686, 77-6687
77-6688, 77-6689, 77-6690, 77-6691, 77-6692
77-6693, 77-6694, 77-6695, 77-6696, 77-6698
77-6702, 77-6733, 77-6743, 77-6794, 77-6795
77-6799, 77-6819, 77-6821, 77-7144
- L D6 B666J J, 77-6697
- L D6 B6666 2AB TJ, 77-6626, 77-6683, 77-6701, 77-6719
77-6720, 77-6721, 77-6722, 77-6723, 77-6724
77-6726, 77-6727, 77-6728, 77-6729, 77-6730
77-6731, 77-6732, 77-6733, 77-6734, 77-6735
77-6736, 77-6737, 77-6738, 77-6739, 77-6740
77-6741, 77-6793, 77-6795, 77-6796, 77-6802
77-6813, 77-6830, 77-7004, 77-7048, 77-7068
77-7144
- L D6 B6666 2AB TJ FQ, 77-6722, 77-6729
- L D6 B6666 2AB TJ GQ HQ, 77-6742
- L D6 B6666 2AB TJ OQ, 77-6729, 77-6730, 77-6731
- L D6 B6666 2AB TJ PQ, 77-6722
- L D6 C6566 1A TJ, 77-6626
- L D6 J6 C666J, 77-6689, 77-6755
- L D6666 B6 2AB TJ, 77-7048
- L E5 B666 FVTTT&J E OQ, 77-6876
- L E5 B666 OV MUTJ A E FQ -B&AEF, 77-6868, 77-7118
77-7162
- L E5 B666 OV MUTJ A E FV1 -B&AEF, 77-6617, 77-6692
77-6695, 77-6868, 77-6875, 77-7159
- L E5 B666TTT&J E FQ F1UU1 OQ, 77-7110, 77-7159
- L E5 B666TTT&J E FQ GQ OQ, 77-7200
- L E5 B666TTT&J E FQ OQ, 77-6618, 77-6692, 77-6695
77-6696, 77-6834, 77-6865, 77-6867, 77-6868
77-6875, 77-7116, 77-7200
- L E6 B666J C, 77-6626
- L E6 D6656 1A T&&T&J R, 77-6678, 77-6679, 77-6680
77-6687, 77-6705, 77-6732, 77-6741, 77-6751
77-6752, 77-6753, 77-6754, 77-6755, 77-6770
77-6793, 77-6800, 77-6833, 77-7004, 77-7047
77-7059, 77-7083, 77-7086, 77-7087, 77-7130
- L G6 D6 B666J, 77-6626, 77-6793
- L545 B4 C5 D 4ABCE J DVTJ-/G 1 O, 77-6820

L6TJ AG BG CG DG EG FG *ALPHA, 77-6818
 L66J CZ, 77-6839
 L666 B6 2AB PJ, 77-6802
 L666 B6 2AB PJ GZ, 77-6775
 MUYZM12 &QV1, 77-6786
 NA2 CR2-O5-Q2, 77-6803
 OCNR, 77-6683
 ONNR&R, 77-6760
 ONNY1&1&Y1&1, 77-6777
 ONN1&R, 77-6770
 ONN1&VO2, 77-6795
 ONN1&1, 77-6611, 77-6612, 77-6629, 77-6658, 77-6715
 77-6717, 77-6769, 77-6770, 77-6771, 77-6772
 77-6773, 77-6774, 77-6775, 77-6776, 77-6788
 77-6794, 77-6800
 ONN2&2, 77-6612, 77-6629, 77-6658, 77-6765, 77-6766
 77-6767, 77-6768, 77-6769, 77-6770, 77-6776
 77-6794, 77-6801
 ONN2GVM2G, 77-6779
 ONN3&3, 77-6770, 77-6776
 ONN4&4, 77-6770, 77-6776
 ONN5&5, 77-6770
 ON1&UN1, 77-6864
 ON1&UN1OV1, 77-6797, 77-6862
 OO, 77-6852
 OOO, 77-6798
 OS1&1, 77-6956, 77-7176, 77-7179
 OVYR XG&R XG, 77-6821
 OV1 & 2-PB-, 77-6805, 77-6811
 QR, 77-6701, 77-6798
 QR BQ DTQ1M1 -LQR BQ DYQ1M1, 77-6653, 77-6747
 QR BQ DYQ1MY -L, 77-6747
 QR DY2& 2U, 77-6602, 77-6615, 77-6867, 77-6868, 77-6869
 77-6870, 77-6871, 77-6872, 77-7157
 QVYZIR CQ DQ -L, 77-6619
 QVYZ2S1, 77-6765
 QVYZ2S2 -DL, 77-6789
 QV1, 77-6929
 QV1 3N, 77-6798
 QV1OR BG CG DVY2&U1, 77-6732
 QV1U1VQ -C, 77-6779
 QV17, 77-6701
 QV3, 77-7179
 QY, 77-6777
 QYYZ1Y -L, 77-6702
 Q1, 77-6775, 77-7055

Q1NUNO&1, 77-6658, 77-6863
 Q2, 77-6610, 77-6775, 77-6798, 77-6862, 77-7148
 Q2G, 77-6824
 Q3, 77-6777
 Q6Q, 77-6764
 R, 77-6819
 SCNR B1, 77-6683
 SCNR2, 77-6683
 SH2Q1Q1SH, 77-6779, 77-6846
 T B3 G6 E666 COT&&T&J F, 77-6697
 T B656 EN HMJ FT B656 EN HMJ F, 77-6802
 T B666 HKJ EZ H2 IR& LZ &E &9/26, 77-6828
 T C666 BN DNVMV INJ B1YQYQYQ1Q L M -BBB
 77-6666
 T C666 BO EV INJ D FZ N G- K-/VM- OT5-16- AN FVN
 IVN LVO PVM SVTJ G J KY N RY 2.
 77-6608, 77-6822, 77-6978
 T D3 B556 BN EM JV MVTIT&J GO1 H1OVZ KZ L
 77-7070
 T D36 I666 B6 2AB U EOT&&&&J, 77-6730
 T D6 B666 CNJ, 77-6684
 T E3 D6 B6666 2AB U FOTT&&&&J HQ IQ, 77-6722
 77-6723, 77-6725, 77-6742
 T E6 D6 B666 NNJ, 77-6626
 T F5 C6 B655 DOV GV OO QO RUT&&TTJ LO1, 77-6614
 77-6658, 77-6667, 77-6668, 77-6669, 77-6670
 77-6672, 77-6793, 77-6801
 T G5 D6 B666 CV HO MO POT&TT&J IYU1 SO1 TO1
 77-6677
 T3OTJ BG, 77-6824
 T3OTJ BR, 77-6753
 T4OVTJ, 77-6793
 T5MN DNJ CZ, 77-6775
 T5MNJ, 77-6775, 77-6862
 T5MTJ, 77-6611
 T5N CSJ BMSWR DZ, 77-6805
 T5NNVJ A BR& DN1&1 E, 77-6717, 77-6813
 T5NTJ ANO, 77-6611, 77-6761, 77-6770
 T5OJ BNW E- ET5N CSJ BMVH, 77-6657, 77-6840
 77-6841, 77-7033
 T5OJ BNW E- ET5N CSJ BMV1, 77-6842, 77-7033
 T5OJ BYVZU1- BT5OJ ENW, 77-6802, 77-6842
 T5OSWTJ, 77-6795
 T5OV EHJ CQ DQ EYQ1Q, 77-6679, 77-6717
 T5VNVJ B2, 77-6779, 77-7185, 77-7189
 T5YNNV EHJ BR DQ& CR& E4, 77-6755
 T56 BM DN FN HNJ IZ, 77-6789

T56 BM DN FNVNVJ F H, 77-6865, 77-7147
 T56 BMJ D2Z GQ, 77-6687
 T56 BN DM FVM INJ, 77-6994
 T56 BN DN FNVNVJ B F H, 77-6903
 T56 BO DO CHJ G3 H1O2O2O4, 77-6796
 T56 BSWMVJ, 77-6681
 T56 BVMSWV &-NA-, 77-6682
 T6MPOTJ BO BN2G2G, 77-6970, 77-7069, 77-7126
 T6MTJ, 77-6611
 T6MVMVJ EF, 77-6608, 77-6863
 T6MVMVJ EN2G2G, 77-6608
 T6N DOTJ ANO, 77-6612, 77-6629, 77-6708, 77-6709
 77-6770
 T6NJ C- BT5MTJ -DL, 77-6707
 T6NJ C- BT5NTJ A, 77-6701, 77-6705, 77-6707, 77-6758
 T6NJ C- BT5NTJ ANO, 77-6706, 77-6707
 T6NJ C- BT6MTJ, 77-6707
 T6NJ CVZ, 77-6768
 T6NTJ ANO, 77-6611, 77-6612, 77-6706, 77-6759, 77-6761
 T6NVMVJ EE A- ET50TJ B1Q CQ -A&C, 77-6956
 T6NVMVJ EF A- ET50TJ B1Q CQ, 77-6608, 77-7002
 T6NVMVJ EI A- ET50TJ B1Q CQ -A&C, 77-6694
 T6NVNJ DZ A- BT50TJ CQ DQ E1Q &GH, 77-6608
 77-7002, 77-7190
 T6MVMV FHJ F2 FR, 77-6678, 77-6732, 77-6753, 77-6770
 77-6789, 77-6833, 77-6837, 77-7200
 T6MVTJ E1YQ- BL6VTJ D F, 77-7022, 77-7184
 T66 BM DN FN HNJ IS- ET5N ONJ DNW, 77-7035
 T66 BN DN GN JNJ CZ EZ HIMR DVMYVQ2VQ
 77-6994
 T66 BN DN GN JNJ CZ EZ H1N1&R DVMYVQ2VQ *L
 L DX
 77-6608
 T66 BNJ BO ENW, 77-6749, 77-6792, 77-6795, 77-6802
 77-6858, 77-6860, 77-6861, 77-7144
 T66 BOVJ, 77-6813
 T66 BVOT&J D GG IVMYVQ1R& JQ, 77-6672
 T7NTJ ANO, 77-6759, 77-6764
 VHH, 77-6774
 VH1YQYQYQ1Q -BAA -D, 77-6929, 77-7181
 VH3VH, 77-7040
 VO2K &5/O, 77-6653
 WNMYUM&N1&NO, 77-6710, 77-6711, 77-6712, 77-6713
 77-6749, 77-6779, 77-6793, 77-6795, 77-7044
 77-7144
 WNMYUM&N2&NO, 77-6710, 77-6711
 WNR BG ENW, 77-6732

WNR DYQY1QMUYGG -DL, 77-6829
 WNR D1G, 77-6732
 WS1&OY, 77-6950
 WS1&O1, 77-6793, 77-6795
 WS1&O2, 77-6793, 77-6795
 ZM1, 77-6854
 ZR, 77-6852
 ZR B D F, 77-6849
 ZR B D- 2, 77-6852
 ZR B DNUNR B, 77-6795, 77-6843, 77-6844
 ZR BQ FVQ, 77-6843
 ZR BR, 77-6795, 77-6840
 ZR BV1, 77-6838
 ZR D-AS-QQO, 77-6811
 ZR DR, 77-6839
 ZR DR DZ, 77-6796, 77-6852, 77-6853
 ZVMQ, 77-6608, 77-6787, 77-7001, 77-7002
 ZVM4, 77-6778
 ZVN1&NO, 77-6779, 77-6780, 77-6781, 77-6782, 77-6783
 77-6784, 77-6792, 77-6795, 77-6797, 77-7142
 ZVN2&NO, 77-6629, 77-6785, 77-6792, 77-6897, 77-7137
 ZVN4&NO, 77-6778
 ZVO2, 77-6878, 77-6879
 ZV1MV1UNN, 77-6850
 ZYUS, 77-6788
 ZZ, 77-6629
 Z1YQR CQ DQ -L, 77-6653, 77-6687
 Z2R CQ DQ, 77-6687
 Z5VQ, 77-7183
 1MM1, 77-6797, 77-6855, 77-6856, 77-6857, 77-7174
 1M1, 77-6611
 1N1&R, 77-6852
 1N1&R DNUNR, 77-6802, 77-6847
 1N1&R DNUNR C, 77-6658, 77-6845, 77-6846, 77-6848
 77-7061, 77-7109
 1N1&R D1U1R, 77-6802
 1N1&R D1U1R -T, 77-6802
 1OSWO1, 77-6792
 1UYG1U1, 77-6819
 1VMR, 77-6813
 1VN1&1, 77-7179
 1VO1U1, 77-6910
 1VV1, 77-6846
 1V1V1, 77-6846

1V2V1, 77-6846

1X&&R BQ E CX, 77-6837

2N2&YUS&S 2, 77-6767, 77-6775

6M6, 77-6763

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